UNITED STATES PATENT APPLICATION OF

KUO-LONG YU
1375 Saylor Court
Zionsville, IN 46077

NICHOLAS MEANWELL
15 Valli Drive
East Hampton, CT 06424

RITA L. CIVIELLO
90 Cow Hill Road
Killingworth, CT 06419

BRIAN LEE VENABLES
26 Stone Manor Drive
Milford, CT 06460

KEITH D. COMBRINK
51 Nicholas Road
Wallingford, CT 06492

YI ZHANG
1106 Hatfield Drive
Evansville, IN 47714

HATICE BELGIN GULGEZE
623 Town Colony Drive
Middletown, CT 06457

BRADLEY C. PEARCE
26 Spice Hill Drive
East Hampton, CT 06424

NY SIN
1655 North Colony Road, Unit 13
Meriden, CT 06450

ZHIWEI YIN
234 Sherman Avenue, Apt. 80
Meriden, CT 06450

XIANGDONG WANG
975 Little Meadow Road
Guilford, CT 06437

JAN WILLEM THURING
760 Mix Avenue, Apt. 7G
Hamden, CT 06514

FOR

HETEROCYCLIC SUBSTITUTED 2-METHYL-BENZIMIDAZOLE ANTIVIRAL AGENTS

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HETEROCYCLIC SUBSTITUTED 2-METHYL-BENZIMIDAZOLE ANTIVIRAL AGENTS

BACKGROUND OF THE INVENTION

1. Field of the Invention

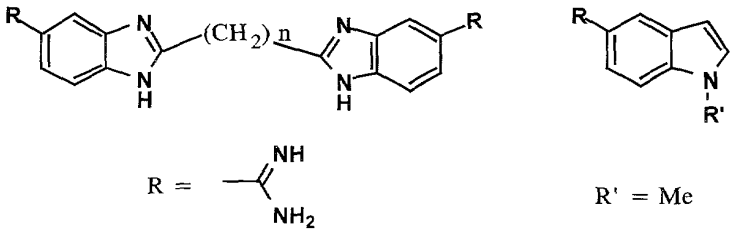
The present invention concerns antiviral compounds, their methods of preparation and their compositions, and use in the treatment of viral infections. More particularly, the invention provides heterocyclic substituted 2-methylbenzimidazole derivatives for the treatment of respiratory syncytial virus infection.

2. Background Art

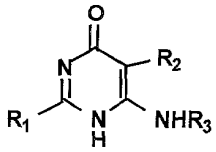
Respiratory syncytial virus (RSV) is the leading cause of serious lower respiratory tract infection in infants, children, elderly and immunocompromised persons. A severe viral infection may result in bronchiolitis or pneumonia which may require hospitalization or result in death. (*JAMA*, 1997, *277*, 12). Currently only Ribavirin is approved for the treatment of this viral infection. Ribavirin is a nucleoside analogue which is administered intranasally as an aerosol. The agent is quite toxic, and its efficacy has remained controversial. RespiGam, approved for prophylaxis in high risk pediatric patients, is an intravenous immunoglobulin which effectively neutralizes the virus. Recently, Synagis, a monoclonal antibody administered through intramuscular injection has also been approved for use in high risk pediatric patients. However, both drugs are very expensive. Accordingly, inexpensive, safe and effective antiviral agents against respiratory syncytial virus will be beneficial for patients.

Many agents are known to inhibit respiratory syncytial virus (De Clercq, *Int. J. Antiviral Agents*, 1996, *7*, 193). Y. Tao et al. (EP 0 058 146 A1, 1998) disclosed that Ceterizine, a known antihistamine, exhibited anti-RSV

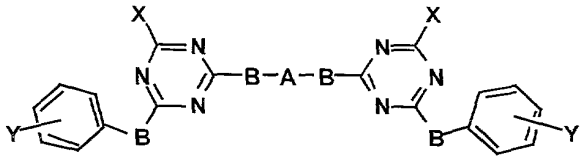
activity. Tidwell et al., *J. Med. Chem.* 1983, *26*, 294 (US Patent 4,324,794, 1982), and Dubovi et al., *Antimicrobial Agents and Chemotherapy,* 1981, *19*, 649, reported a series of amidino compounds with the formula shown below as inhibitors of RSV.



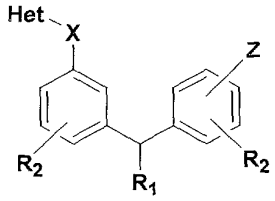
Hsu et al., US Patent 5,256,668 (1993) also disclosed a series of 6-aminopyrimidones that possess anti-viral activity against RSV.



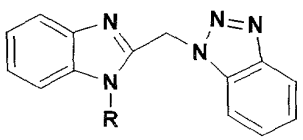
Y. Gluzman, et al., (AU Patent, Au-A-14,704, 1997) and P. R. Wyde et al. (*Antiviral Res.* 1998, *38*, 31) disclosed a series of triazine containing compounds that were useful for the treatment and/or prevention of RSV infection.

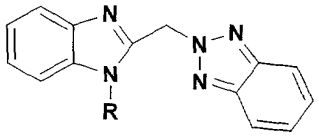


In addition, T. Nitz, et al., (WO Patent, WO 00/38508, 1999) disclosed a series of triaryl containing compounds that were useful for the treatment and/or prevention of RSV and related pneumoviral infections.

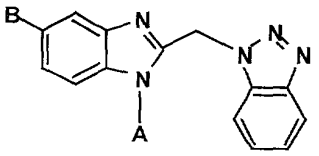


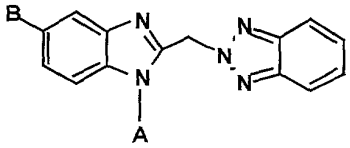
Moreover, Yu et al. (WO 020004900) also disclosed a series of substituted benzimidazoles that is useful for the treatment and prevention of RSV infection.





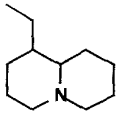
A related series of compounds were first disclosed by F. Pagani and F. Sparatore in *Boll Chim Farm.* 1965, *104,* 427 and by G. Paglietti, et al. in *Il Farmaco, Ed. Sci.* 1975, *30*, 505, and found to possess analgesic and anti-arrhythmic activity. The structural formula for these compounds are depicted in Formula Ia and Ib.





Formula Ia Formula Ib

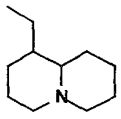
In Formula Ia and Ib, A is $-(CH_2)n-N(R)_2$, n = 2 or 3, R = Me or Et,

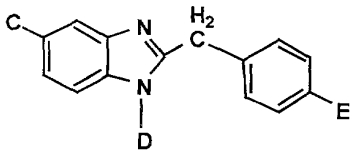
or A is 

; B = H, Cl, CF_3, CH_3CO, NO_2.

Another series of closely related compounds that Sparatore had disclosed were in *Il Farmaco Ed. Sci.* 1967, *23*, 344 (US patent 3,394, 141, 1968). Some

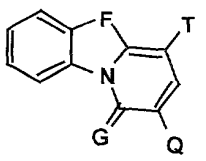
of the compounds were reported to have analgesic, anti-inflammatory or anti-pyretic activities. The structure of these compounds is depicted in Formula Ic. In Formula Ic, C = H, CF_3, or NO_2. D is -(CH_2)n-NR_2, n = 2 or 3, R = Me or Et, or

D =  ; E is H, Cl or OEt.

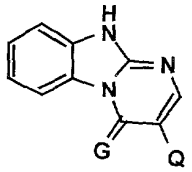


Formula Ic

Another series of compounds structurally related to this invention are pyrido[1,2-a]benzoazoles and pyrimidio[1,2a]benzimidazoles disclosed by S. Shigeta et al in *Antiviral Chem. & Chemother.* 1992, *3*, 171. These compounds have demonstrated inhibition of orthomyxovirus and paramyxovirus replication in HeLa cells. The structures of these compounds are shown in Formulas Id and Ie, in which F = NH, S, or O; Q = -NHCOPh, -COOH, COOEt, or CN; T = COMe, CN, or COOEt; G = O or NH.



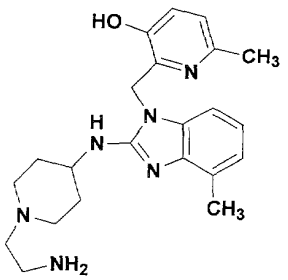
Formula Id



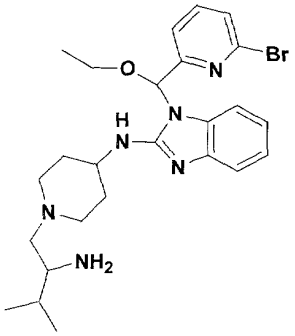
Formula Ie

A bis-benzimidazole with an ethylenediol linker shown below has also been reported as a potent inhibitor of rhinoviruses (Roderick, et al. *J. Med. Chem.* 1972, *15*, 655).

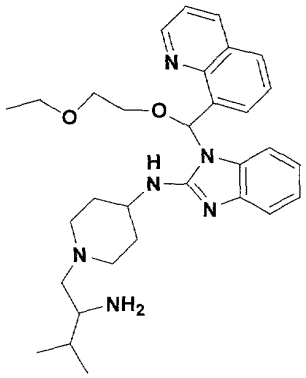
A series of 2-aminobenzimidazoles have been reported by E. Janssens, et al. as inhibitors of RSV in a series of recent publications and representative examples formula 1f-1h are shown below from PCT WO 01/00611 A1; PCT WO 01/00612 and PCT WO 01/00615, respectively all published on January 4, 2001.



Formula 1f

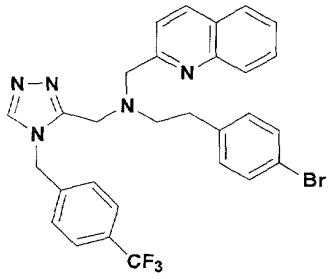


Formula 1g

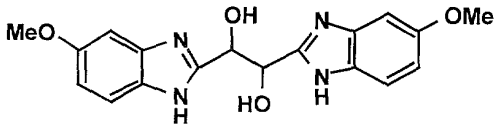


Formula 1h

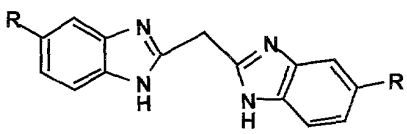
A series of triazole containing compounds have been reported by Janssen as inhibitors of RSV in PCT WO 01/36395 (May 25, 2001) and a representative example is shown below.



Formula 1i

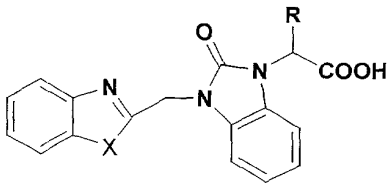


Other structurally related compounds are bis-benzimidazoles which possess antifungal activity (B. Cakir, et al. *Eczacilik Fak. Derg.* 1988, *5*, 71).



R = H, NO_2

Also, H. R. Howard et al. reported a series of benzimidazolone-1-acetic acids that possessed aldolase reductase inhibitory activity (*Eur. J. Med. Chem.* 1992, *27*, 779-789).



X = O, S

Other prior art related to the chemical structure of the present invention:

(1) F. Sparatore, et al, "Derivati Benzotriazolici Attivi Sull'accrescimento Delle Piante," *Il Farmaco Ed. Sci.* 1978, *33*, 901.

(2) Katritzky, A. R. et al, "Synthesis and Transformations Of Substituted Benzazolyl- and Tetrazolyl(benzotriazol-l-yl)methanes," *J. Heterocyclic Chem.* 1996, *33*, 1107.

(3) Terri A. Fairley, et al. " Structure, DNA Minor Groove Binding, And Base Pair Specificity of Alkyl and Aryl-Linked Bis(amidinobenzimidazoles) and Bis(amidinoindoles), *J. Med. Chem.* 1993, *36*, 1746.

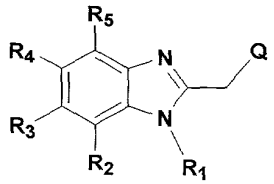
(4) R. K. Upadhyay et al, " New Synthesis and Biological Evaluation," *Indian J. Heterocyclic Chem.* 1994, *4*, 121.

(5) A. R. Katritzky, et al, " A New Route to N-substituted Heterocycles," *Tetrahedron*, 1993, *49*, 2829.

(6) K. Yu et al. in Substituted Benzimidazole Anti-viral Agents, PCT WO00/04900 published February 3, 2000.

SUMMARY OF THE INVENTION

This invention relates to novel heterocyclic substituted 2-methylbenzimidazoles and the antiviral activity against RSV. The structural formula for these compounds are depicted in Formula I, and includes pharmaceutically acceptable salts thereof,



Formula I

wherein:

R_1 is $-(CR^aR^b)_n-X$;

R^a, R^b are each independently selected from the group consisting of H, C_{1-6} alkyl; each of said C_{1-6} alkyl being optionally substituted with one to six same or different halogen;

X is H or C_{1-6} alkyl; said C_{1-6} alkyl being optionally substituted with a member selected from the group consisting of (1) one to six same or different halogen or hydroxy, (2) heteroaryl, (3) non-aromatic heterocyclic ring and (4) a member selected from Group A;

n is 1-6;

Group A is a member selected from the group consisting of halogen, CN, OR^x, $N^+R^cR^dR^e[T^-]$, NR^cR^d, COR^c, CO_2R^x, $CONR^xR^y$ and $S(O)_mR^c$;

R^x and R^y are independently H or C_{1-6} alkyl;

R^c, R^d and R^e are independently C_{1-6} alkyl;

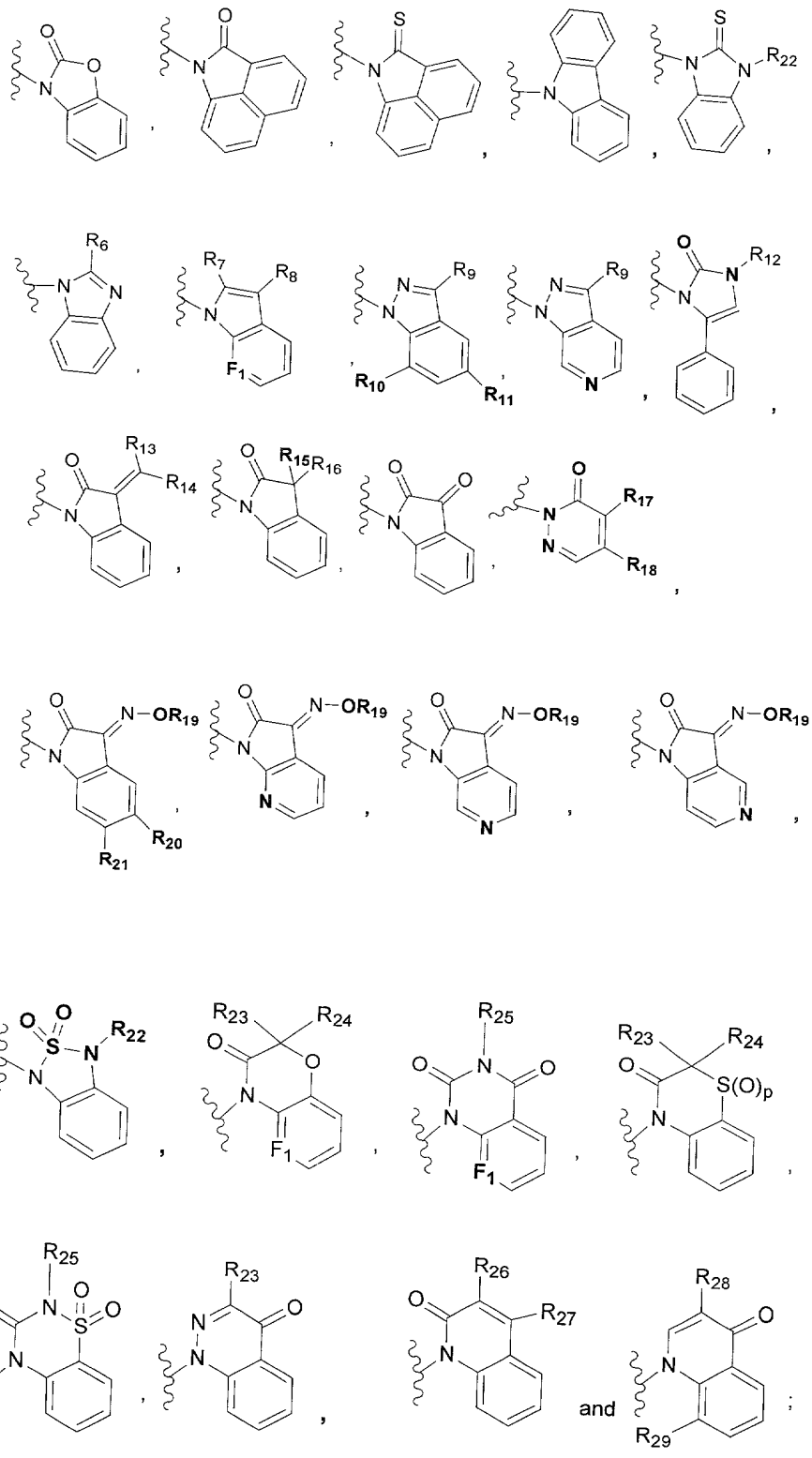
m is 0-2

T^- is halogen, $CF_3SO_3^-$ or $CH_3SO_3^-$;

R_2 and R_5 are independently halogen or H;

R_3 and R_4 are each independently selected from the group consisting of H, halogen and C_{1-6} alkyl; said C_{1-6} alkyl can be optionally substituted with one to six same or different halogen;

Q is a member selected from the group consisting of



F_1 is CH or N;

R_6 is selected from the group consisting of H, halogen, NR^fR^g, SR^n and a five-membered heteroaryl containing one to two of the same or different heteroatoms selected from the group consisting of O, S and N;

R^f and R^g are independently H, C_{1-6} alkyl or C_{1-6} alkyl; said C_{1-6} alkyl optionally substituted with OR^h or CO_2R^h;

R^h and R^j are independently H or C_{1-6} alkyl;

R^n is C_{1-6} alkyl optionally substituted with CO_2R^h;

R_7 is H, or CO_2R^h;

R_8 is H, COR^h, CO_2R^h or C_{1-6} alkyl; said C_{1-6} alkyl optionally substituted with OR^h;

R_9 is H, halogen, heteroaryl, phenyl, phenyl substituted with a halogen group, phenyl substituted with a methanesulfonyl group, COR^h, CO_2R^h, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-4} alkynyl; said C_{2-4} alkynyl optionally substituted with C_{1-6} cycloalkyl;

R_{10} and R_{11} are independently H, NO_2 or NR^hR^i

R_{12} is H, CO_2R^h or C_{1-2} alkyl; said C_{1-2} alkyl optionally substituted with phenyl;

R_{13} and R_{14} are independently selected from the group consisting of H, OR^h, $CONR^jR^k$, NR^lR^m and pyrrolidine; wherein said pyrrolidine is attached at the nitrogen atom;

R^j and R^k are independently H or C_{1-6} alkyl optionally substituted with phenyl;

R^l and R^m are independently C_{1-6} alkyl;

R_{15} and R_{16} are independently selected from the group consisting of H, OR^h, phenyl, pyridyl and C_{1-6} alkyl; said C_{1-6} alkyl optionally substituted with CO_2R^h;

R_{17} and R_{18} are independently selected from the group consisting of halogen, NR^lR^m, SR^h and morpholine; wherein said morpholine is attached at the nitrogen atom;

R_{19} is selected from the group consisting of H, phenyl, C_{2-6} alkenyl and C_{1-6} alkyl; said C_{1-6} alkyl optionally substituted with one to six same or different halogen, CO_2R^h, $CONR^hR^i$, pyridyl and one to three phenyl groups; wherein in the case of C_{1-6} alkyl substituted with one phenyl group, said phenyl group is optionally substituted with a member selected from the group consisting of halogen, $PO(OR^h)_2$, CO_2R^h, SO_2R^n and $CONR^hR^i$;

R^n is C_{1-6} alkyl;

R_{20} and R_{21} are independently H or halogen;

R_{22} is C_{1-6} alkyl;

R_{23} and R_{24} are independently H or C_{1-6} alkyl;

R_{25} is C_{1-6} cycloalkyl or C_{1-6} alkyl; said C_{1-6} alkyl group optionally substituted with a member selected from the group consisting of CO_2R^h, $PhCO_2R^h$ and one to six same or different halogens;

R_{26} is selected from the group consisting of H, halogen, C_{1-6} alkyl; C_{2-6} alkenyl, OR^h and COR^h; said C_{2-6} alkenyl being optionally substituted with OR^h;

R_{27} is H, OR^h or CO_2R^h;

R_{28} is CO_2R^h;

R_{29} is H or halogen;

heteroaryl is a 5- or 6-membered aromatic ring containing at least one and up to four non-carbon atoms selected from the group consisting of O, N and S;

non-aromatic heterocyclic ring is a 3 to 7-membered non-aromatic ring containing at least one and up to four non-carbon atoms selected from the group consisting of O, N and S; and

p is 0-2.

In a preferred embodiment, heteroaryl is selected from the group consisting of pyridyl, thiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-oxadiazol-5-one and tetrazole.

In another preferred embodiment, non-aromatic heterocyclic ring is selected from the group consisting of pyrrolidine and piperidine.

R^a and R^b are hydrogen.

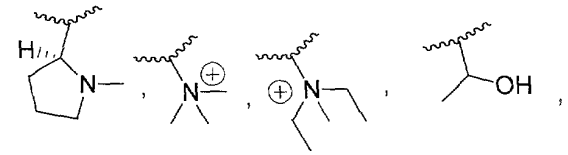
In another preferred embodiment, R_1 is $-(CH_2)_n$-X and n is 2-4.

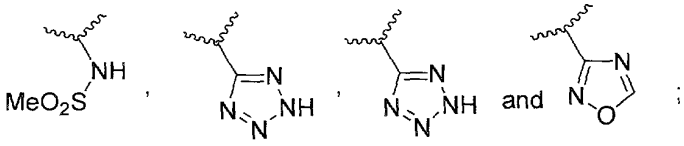
In another prefrred embodiment, R_3 and R_4 are each independently selected from the group consisting of H, fluorine and C_{1-2} alkyl; said C_{1-2} alkyl being optionally substituted with one to three fluorine atoms.

In another preferred embodiment R_1 is 3-methyl-2-butyl or $-(CH_2)_n$-X wherein n is 2-4;

X is a member selected from the group consisting of

-F, -CN, -SR^c, -SO_2R^c, -OR^x, -COR^c ,CO_2R^x, $CONR^xR^y$, $[NR^cR^dR^e][T^-]$,





R^c, R^d and R^e are independently C_{1-4} alkyl; and

R^x and R^y are independently H or C_{1-4} alkyl.

In another preferred embodiment, R_2 and R_5 are independently H.

Another preferred embodiment includes a pharmaceutical composition which comprises a therapeutically effective amount of one or more of the aforementioned compounds of Formula I, including pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

Another preferred embodiment includes method for treating mammals infected with RSV, and in need thereof, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I, including pharmaceutically acceptable salts thereof.

The term pharmaceutically aceptable salt includes solvates, hydrates, acid addition salts and quarternary salts. The acid addition salts are formed from a compound of Formula I and a pharmceutically acceptable inorganic acid including but not limited to hydrochloric, hydrobromic, sulfuric, phosphoric,

methanesulfonic, acetic, citric, malonic, fumaric, maleic, sulfamic, or tartaric acids. Quaternary salts include chloride, bromide, iodide, sulfate, phosphate, methansulfonate, citrate, acetate, malonate, fumarate, sulfamate, and tartrate.

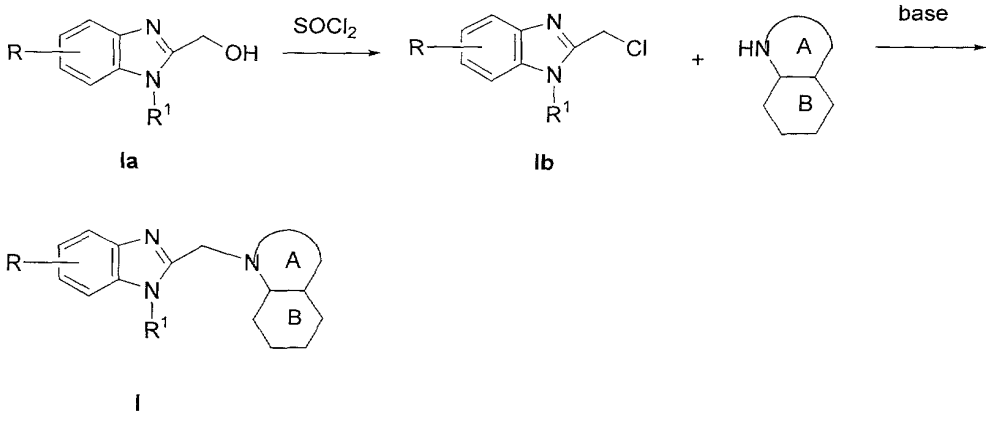
Halogen means bromine, chlorine, iodine and fluorine.

DETAILED DESCRIPTION OF THE INVENTION

Compounds of Formula I may be prepared using the procedures outlined in Schemes I-X.

Compounds of Formula I can be prepared as shown in Scheme I. Treatment of substituted or unsubstituted 2-hydroxymethylbenzimidazole Ia with thionyl chloride provides 2-chloromethylbenzimidazole Ib. Coupling of chloride Ib with a heterocycle in the presence of base, preferred cesium carbonate, sodium hydride, or phosphazene base such as BTPP gives compounds of Formula I.

Scheme I

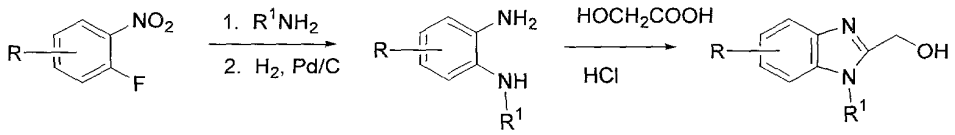


Ia Ib I

The synthesis of compounds of Formula Ia is described in Schemes Ia and Ib. Coupling of substituted or unsubstituted 2-fluoro-nitrobenzene (III) with an appropriate amine followed by reduction under catalytic hydrogenation conditions gives diamines of Formula IV. Cyclization of diamine IV with

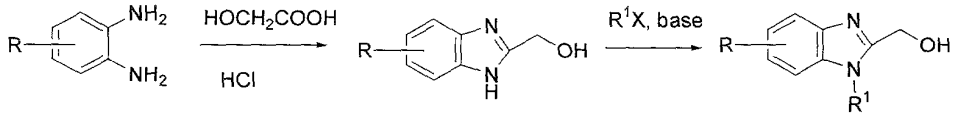
glycolic acid in 4-6 N HCl gives compounds of Formula Ia (Scheme Ia). Alternatively, a diamine of Formula V can be cyclized with glycolic acid in 4-6 N HCl to give 2-hydroxymethyl benzimidazole VI which is treated with base preferably cesium carbonate or sodium hydride followed by the addition of an appropriate halide to give compound Ia (Scheme Ib).

Scheme Ia



III IV Ia

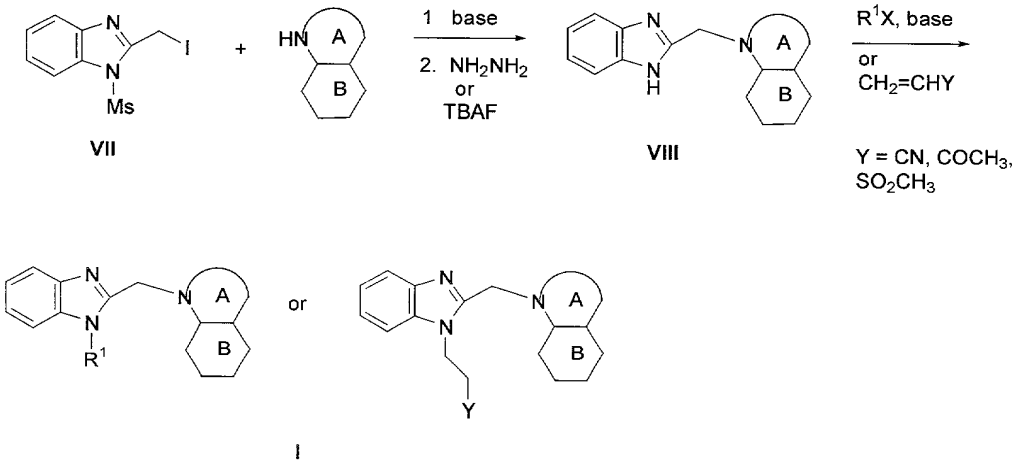
Scheme Ib



V VI Ia

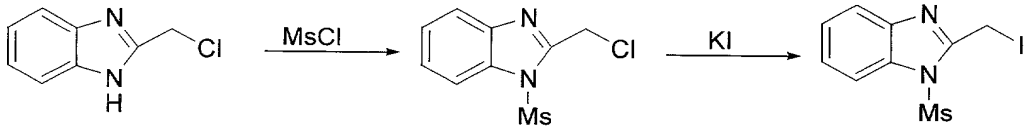
Compounds of Formula I can also be prepared as shown in Scheme II. Coupling of the mesylate VII and an appropriate heterocycle in the presence of base such as sodium hydride or BTPP followed by cleavage of the mesylate with tetrabutylammonium fluoride or hydrazine gives intermediate VIII. Alkylation of compound VIII with an appropriate halide in the presence of base such as sodium hydride, BTPP or cesium carbonate gives compound of Formula I. Alternatively, compounds of Formula I can be obtained through a Michael addition of VIII with acrylonitrile, methyl vinyl ketone, or methyl vinyl sulfone.

Scheme II



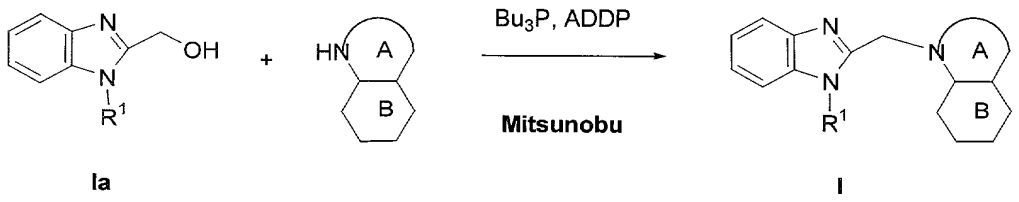
The compound VII can be prepared using the reaction sequence depicted in Scheme IIa. In Scheme IIa, 2-chloromethylbenzimidazole reacts with methanesulfonyl chloride (MsCl) and triethylamine to give compound of Formula VIIa. The chloride can be refluxed with potassium iodide in acetone to produce the compound of Formula VII, as described in PCT WO 00/04900.

Scheme IIa



Alternatively, compounds of Formula I can be obtained through Mitsunobu coupling of Ia with an appropriate heterocycle in the presence of tributylphosphine and 1,1'-(azodicarbonyl)dipiperidine (ADDP) as depicted in Scheme III.

Scheme III



Ia I

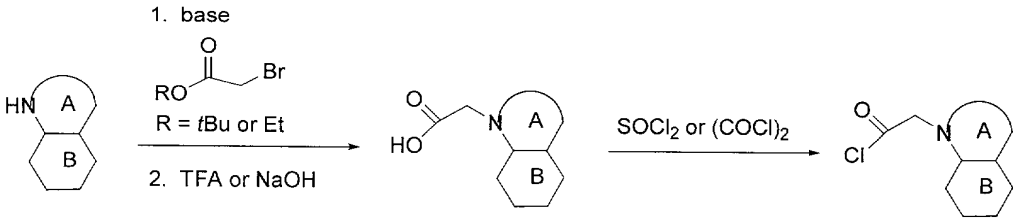
In a different approach, compounds of Formula I were prepared using the synthetic route illustrated in Scheme IV. The diamine IV is first coupled either with acid IXa through an amide coupling reagent such as EDAC and HOBT or 2-chloro-1-methyl pyridinium iodide or with acid chloride IXb in the prescence of base. The crude intermediate is directly cyclized to the benzimidazole in refluxing acetic acid providing compounds of Formula I.

Scheme IV

IV X = OH IXa Cl IXb I

Scheme IVa describes the synthesis of compounds of formulas IXa and IXb. An appropriate heterocycle is alkylated with either *t*-butyl bromoacetate or ethyl bromoacetate followed by hydrolysis of the ester with trifluoroacetic acid or sodium hydroxide gives acid IXa. Conversion of the acid to the acid chloride with thionyl chloride or oxalyl chloride provides a compound of Formula IXb.

Scheme IVa

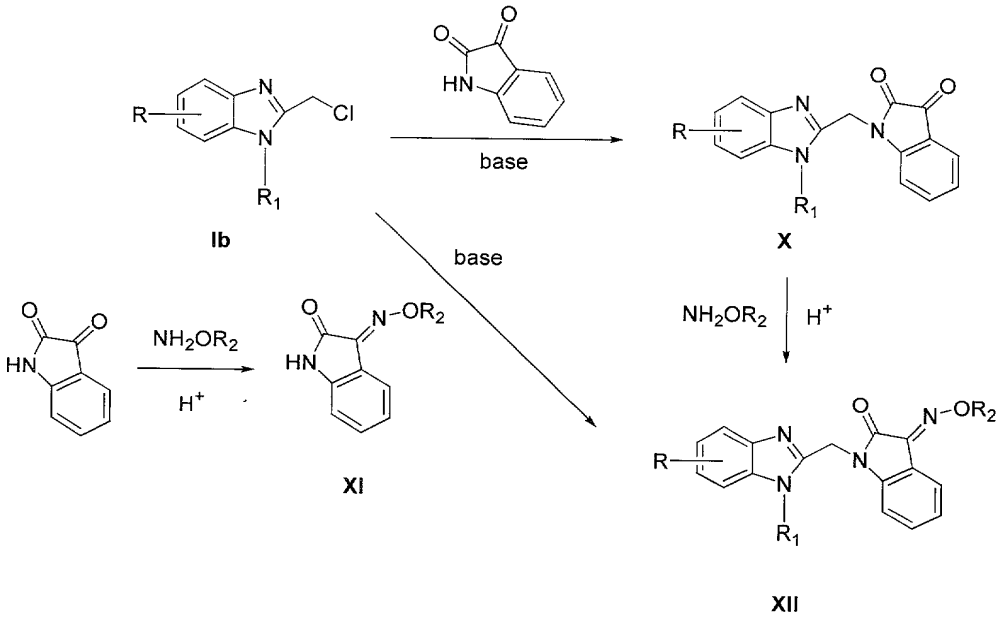


IXa IXb

Some compounds of Formula I can be further derivatized with a specific example being the isatin and oxime series. Derivative compounds of Formula XII can be prepared as outlined in Schemes V, VI, and VII.

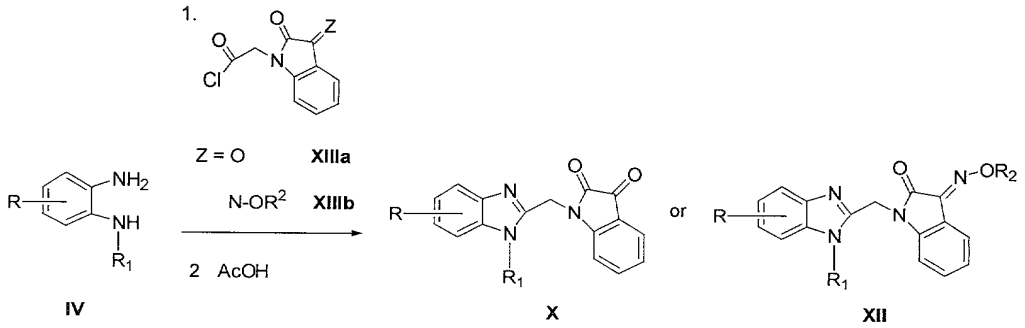
In Scheme V, chloride Ib reacts with isatin in the presence of a base, such as sodium hydride or BTPP, to give compounds of Formula X. The isatin derivative X and an appropriate hydroxylamine are refluxed with an acid catalyst to provide oximes of Formula XII. The chloride Ib also can react directly with an oxime of Formula XI to afford compounds of Formula XII.

Scheme V

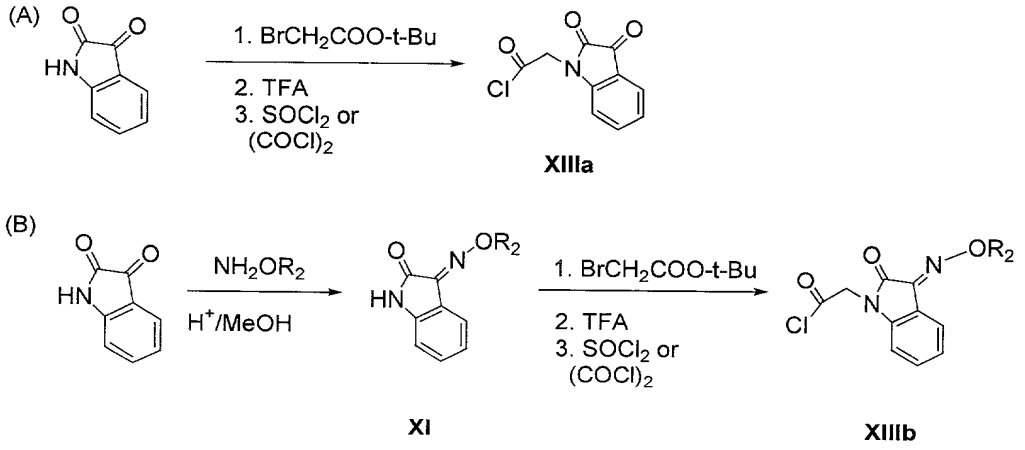


Alternatively, phenylenediamine of Formula IV was coupled to an isatin or oxime acetyl chloride of Formula XIIIa or XIIIb, followed by ring closure in refluxing acetic acid to provide compounds of Formula X or XII (Scheme VI). The corresponding isatin or oxime acetyl chloride intermediates XIIIa or XIIIb were synthesized using standard procedures as shown in Scheme VIa.

Scheme VI

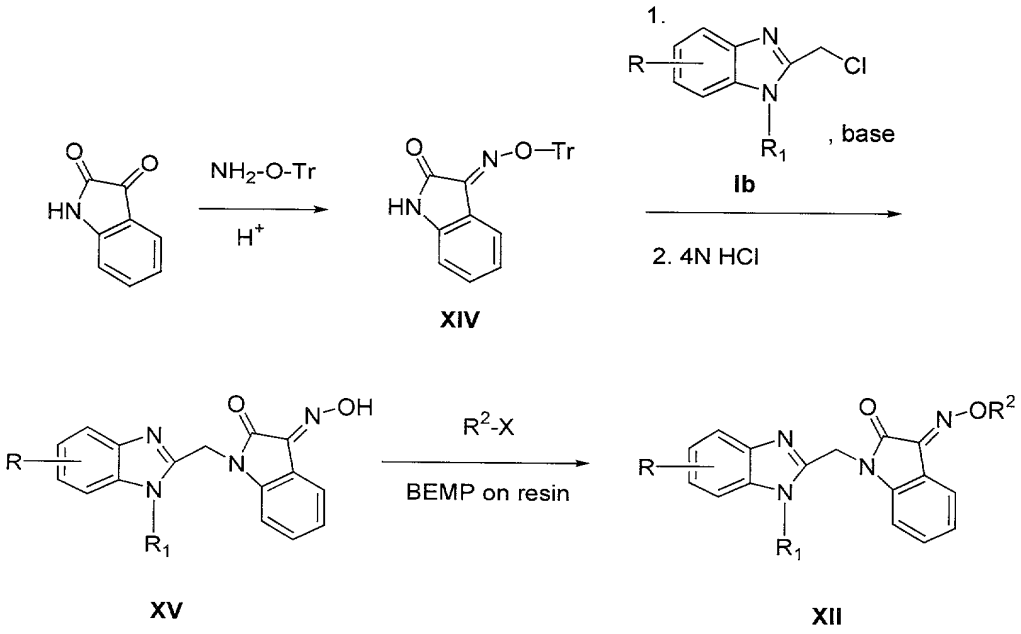


Scheme VIa



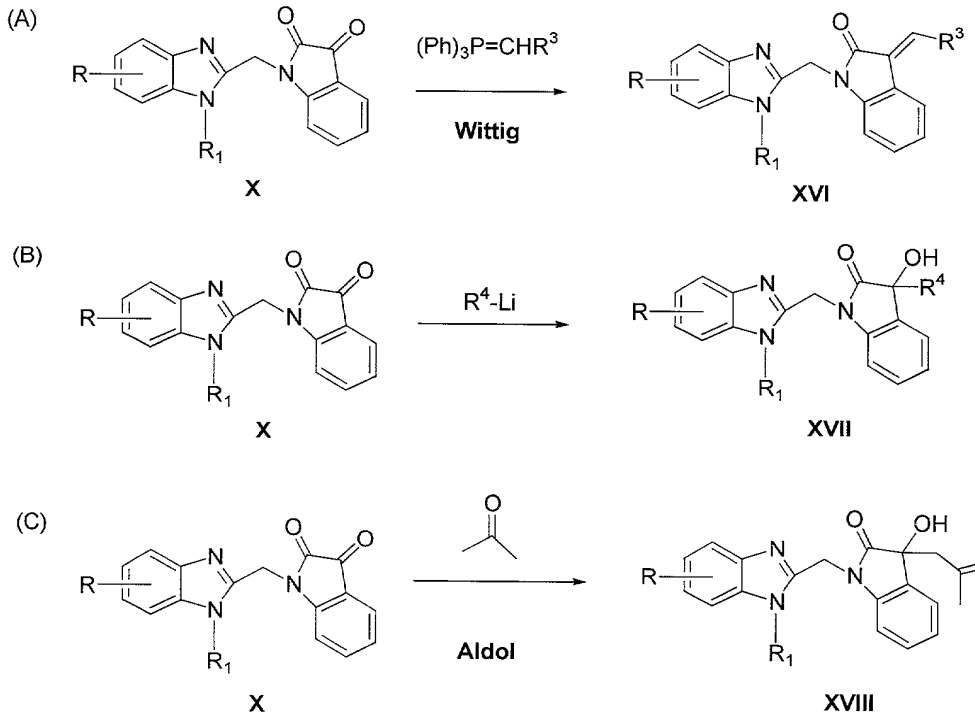
In an alternative approach depicted in Scheme VII, isatin is refluxed with O-tritylhydroxylamine. The resulting oxime XIV is coupled to chloride Ib and subsequently hydrolyzed to give oxime derivative of Formula XV. Alkylation of the oxime with an appropriate halide in the presence of BEMP on polystyrene yields compounds of Formula XII.

Scheme VII

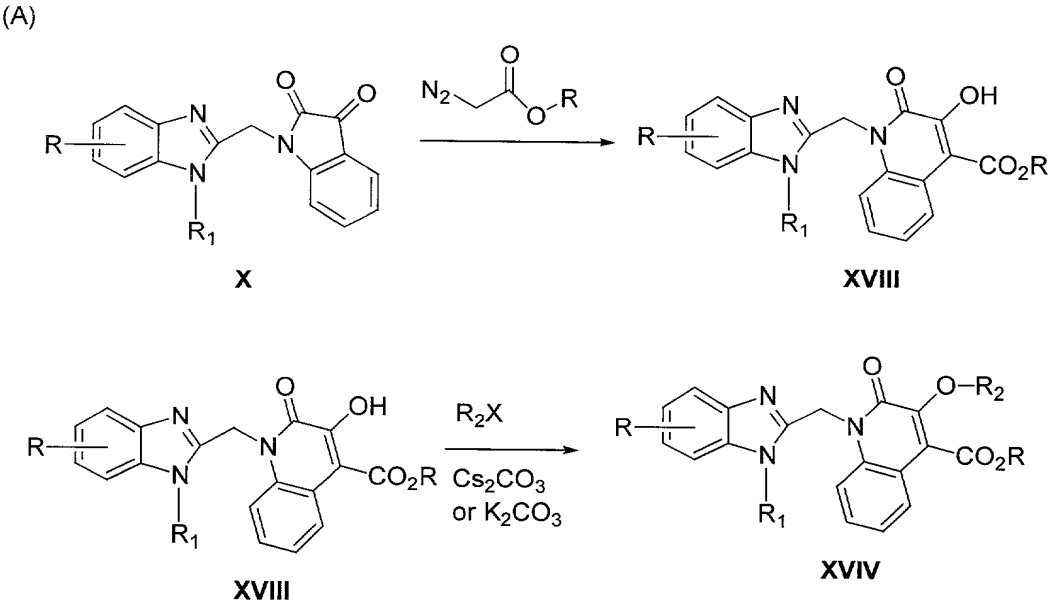


In addition to oxime derivatives, isatin compound X can be converted to derivatives XVI, XVII, and XVIII through Wittig reaction, reaction with organolithium reagent, or Aldol condensation as depicted in Scheme VIII.

Scheme VIII

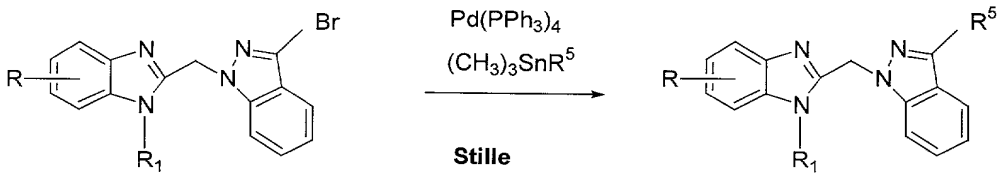


In addition, compounds of Formula X can be converted to 2-quinolone derivatives by reaction of the isatin X with ethyl diazoacetate to give derivative XIX.



Compound of Formula XXII, prepared according to Scheme I, II, III, or IV, can be further derivatized through Stille coupling as shown in Scheme IX.

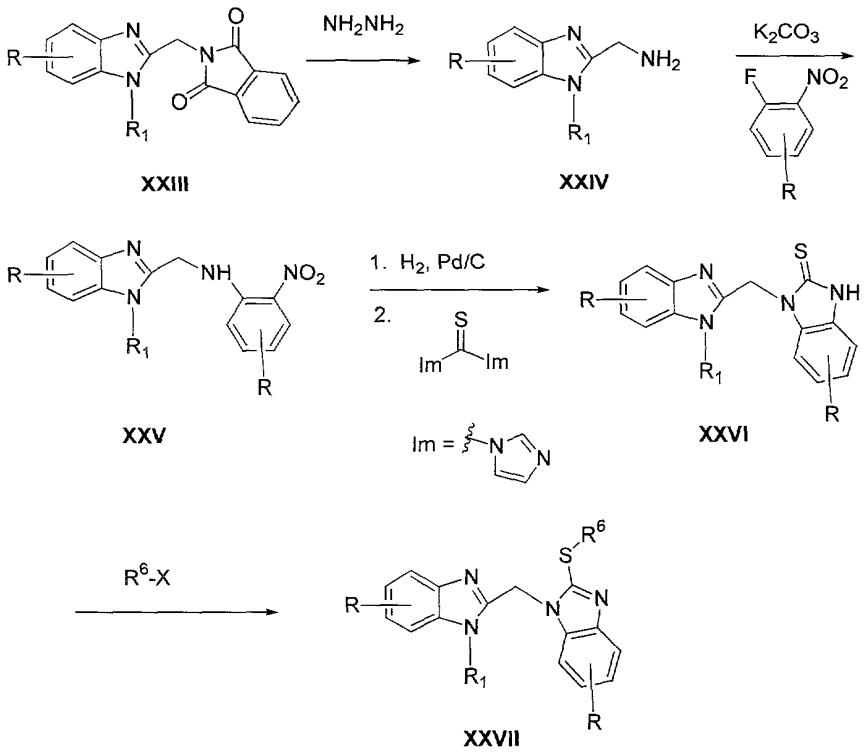
Scheme IX



XXI XXII

Derivatives of Formula XXIV are prepared by formation of the heterocyclic ring as described in Scheme X. Compound XXIII, prepared according to Scheme I with phthalimide as the heterocycle, is treated with hydrazine to afford the amine XXIV which is coupled to a 2-fluoro-nitrobenzene. Reduction under catalytic hydrogenation conditions followed by cyclization with 1,1'-thiocarbonyldiimidazole provides compound of Formula XXVI which can be further derivatized by alkylation with an appropriate halide to compound XXVII.

Scheme X



Abbreviations used in Schemes I-X and experimental section:

AcOH: glacial acetic acid

BEMP: 2-*t*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine

BTPP: *t*-butylimino-tri(pyrrolidino)phosphorane

DIEA: *N,N*-diisopropylethylamine

DMF: dimethylformamide

EDAC: 1-[3-(dimethyl amino)propyl]-3-ethylcarbodiimide hydrochloride

EtOH: ethyl alcohol

EtOAc: ethyl acetate

Et_2O: diethyl ether

HOBT: 1-hydroxybenzotriazole hydrate

MeOH: methyl alcohol

Ph: phenyl

Prep HPLC: preparative high performance liquid chromatography

TFA: trifluoroacetic acid

THF: tetrahydrofuran.

Tr: trityl or triphenylmethyl

TBDMS: *t*-butyldimethylsilyl

TMS: trimethylsilyl

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

It will be further appreciated that the amount of a compound of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician or veterinarian. In general however, a suitable dose will be in the range of from about 0.01 to 750 mg/kg of body weight per day preferably in the range of 0.1 to 100 mg/kg/day, most preferably in the range of 0.5 to 25 mg/kg/day.

Treatment is preferably commenced before or at the time of infection and continued until virus is no longer present in the respiratory tract. However, the treatment can also be commenced when given post-infection, for example after the appearance of established symptoms.

Suitable treatment is given 1-4 times daily and continued for 3-7, e.g. 5 days post infection depending upon the particular compound used.

The desired dose may be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The compound is conveniently administered in unit dosage form, for example, containing 10 to 1500 mg, conveniently 20 to 1000 mg, most conveniently 50 to 700 mg of active ingredient per unit dosage form.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of the Formula I, or a pharmaceutically acceptable salt or derivative thereof together with a pharmaceutically acceptable carrier thereof.

The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical formulations may be in the form of conventional formulations for the intended mode of administration.

For intranasal administration according to the method of the invention the compounds of the invention may be administered by any of the methods and formulations employed in the art for intranasal administration.

Thus in general the compounds may be administered in the form of a solution or a suspension or as a dry powder.

Solutions and suspensions will generally be aqueous, for example prepared from water alone (for example sterile or pyrogen-free water), or water and a physiologically acceptable co-solvent (for example ethanol, propylene glycol, and polyethylene glycols such as PEG 400).

Such solutions or suspensions may additionally contain other excipients, for example, preservatives (such as benzalkonium chloride), solubilizing

agents/surfactants such as polysorbates (e.g. Tween 80, Span 80, benzalkonium chloride), buffering agents, isotonicity-adjusting agents (for example sodium chloride), absorption enhancers and viscosity enhancers. Suspensions may additionally contain suspending agents (for example microcrystalline cellulose, carboxymethyl cellulose sodium).

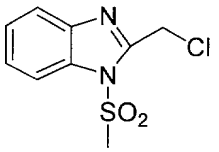
Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case a means of dose metering is desirably provided. In the case of a dropper or pipette this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomizing spray pump.

Intranasal administration may also be achieved by means of an aerosol formulation in which the compound is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC), for example dichlorodifluoromethane, trichlorofluoromethane or dichlorotetrafluroroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Experimental Section

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance 500, AC-300, Bruker DPX-300 or a Varian Gemini 300 spectrometer. All spectra were determined in $CDCl_3$, CD_3OD, d-acetone or DMSO-d_6 and chemical shifts are reported in δ units relative to tetramethylsilane (TMS). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad peak; dd, doublet of doublets; dt, doublet of triplets. Mass spectroscopy was performed on a Finnigan SSQ 7000 quadrupole mass spectrometer in both positive and negative electrospray ionization (ESI) modes or

on a LC-MS using Shimadzu LC-10AS with micromass platform LC single quadrupole mass spectrometer in positive electrospray ionization. High resolution mass spectroscopy was recorded using Finnigan MAT 900. Infrared (IR) spectra were recorded on a Perkin-Elmer system 2000 FT-IR. Elemental analysis was performed with Perkin-Elmer series II, model 2400 CHN/O/S analyzer. Column chromatography was performed on silica gel from VWR Scientific. Preparative HPLC was performed using Shimadzu LC-8A on a C18 column eluted with mixture of MeOH in water with 0.1 % trifluoroacetic acid.



1a

To a solution of 2-(chloromethyl)benzimidazole (80 g, 0.48 mol) and methanesulfonyl chloride (58.3 mL, 0.75 mol) in methylene chloride (0.5 L), triethylamine (136 mL, 0.97 mol) was added dropwise under nitrogen. The resulting mixture was stirred at room temperature for 6 hours. The mixture was filtered and the filtrate was evaporated. The residue was triturated in methanol and filtered to afford 74.9 g of compound **1a** as a brown solid:

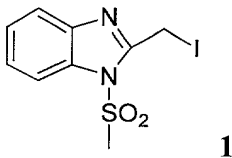
^{1}H NMR ($CDCl_3$) δ 3.44 (s, 3 H), 5.11 (s, 2 H), 7.40-7.49 (m, 2 H), 7.76-7.82 (m, 1 H), 7.85-7.91 (m, 1 H);

IR (KBr, cm^{-1}) 3027, 2920, 1371, 1349, 1177, 1144, 1059;

MS m/e 245 (MH^+);

Anal. Calcd for $C_9H_9ClN_2O_2S$: C, 44.18; H, 3.71; N, 11.45

Found: C, 44.09; H, 3.57; N, 11.49.



1b

A solution of potassium iodide (206 g, 1.24 mol) and compound **1a** (74.8 g, 0.414 mol) in acetone (1 L) was stirred at reflux under nitrogen for 4 hours. The solid was filtered and the filtrate was evaporated. The crude product was triturated in MeOH and filtered to give 83 g of compound **1b** as a solid:

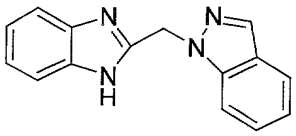
^{1}H NMR ($CDCl_3$) δ 3.48 (s, 3 H), 4.97 (s, 2 H), 7.40-7.50 (m, 2 H), 7.75-7.85 (m, 2 H);

IR (KBr, cm^{-1}) 3022, 2916, 1366, 1173, 1055, 966, 763, 745;

MS m/e 336 (MH^+);

Anal. Calcd for $C_9H_9IN_2O_2S$: C, 32.16; H, 2.70; N, 8.33

Found: C, 32.05; H, 2.63; N, 8.22.

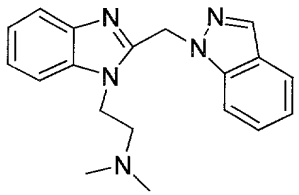


1c

To a solution of indazole (591 mg, 5.00 mmol) in DMF (7 mL) was added NaH (60% suspension in mineral oil, 200 mg, 5.00 mmol). After stirring for 30 minutes, compound **1b** (1.51 g, 4.50 mmol) was added and the resulting solution was stirred at room temperature overnight. The mixture was diluted with saturated aqueous $NaHCO_3$, and extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and evaporated. Purification by flash column chromatography (gradient, EtOAc:hexanes = 1:4 to 2:1) gave an intermediate which was subsequently treated with hydrazine (2 mL) in MeOH (10 mL) and stirred at 65°C for 2 hours. The solvent was evaporated and the residue was purified by column chromatography (gradient, EtOAc:hexanes = 1:1 to straight EtOAc to EtOAc:MeOH = 10:1). Recrystallization from EtOAc and hexanes gave 359mg (29% yield) of compound **1c**:

^{1}H NMR ($CDCl_3$) δ 5.88 (s, 2 H), 7.20 (t, J = 4.5 Hz, 1 H), 7.24-7.27 (m, 2 H), 7.41 (t, J = 4.5 Hz, 1 H), 7.55 (bs over d, J = 5.2 Hz, 2 H), 7.75 (d, J = 4.9 Hz, 1 H), 8.11 (s, 2 H);

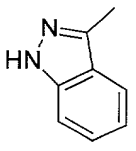
MS m/e 249 (MH^+).



1

To a mixture of compound **1c** (248 mg, 1.00 mmol) and NaH (60% suspension in mineral oil, 96 mg, 2.40 mmol) in DMF (3 mL) was added 2-chloro-N,N-dimethylethylamine hydrochloride (158 mg, 1.10 mmol) and the mixture was stirred at 65°C for 4 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and evaporated. The resulting residue was purified by flash column chromatography (gradient, EtOAc:hexanes = 1:1 to straight EtOAc to EtOAc:MeOH = 10:1) to give 27 mg (14% yield) of compound **1** as a light yellow gum:

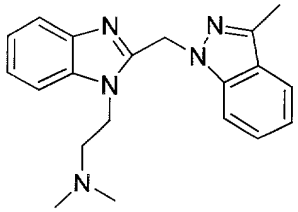
^1H NMR ($CDCl_3$) δ 2.24 (bs, 8 H), 4.29 (bt, J = 6.8 Hz, 2 H), 5.90 (s, 2 H), 7.07 (t, J = 7.7 Hz, 1 H), 7.19-7.29 (m, 4 H), 7.62 (t, J = 7.6 Hz, 2 H), 7.71-7.75 (m, 1 H), 7.96 (s, 1 H);
IR (KBr, cm^{-1}) 2944, 2772, 1616, 1464, 1418, 1333, 1164, 743;
MS m/e 320 (MH^+).



2a

A mixture of 2'-bromoacetophenone (2.00 g, 10.05 mmol) and hydrazine (322 mg, 10.05 mmol) in EtOH (10 mL) was refluxed for 48 hours. The solvent was evaporated. To the residue in THF (75 mL) was added 1 N HCl (15 mL). The resulting emulsion was warmed and stirred for 10 minutes. The mixture was

neutralized with saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated. The residue was subjected to column chromatography (EtOAc/hexanes, 1:1) to give 363 mg (27% yield) of compound **2a** which was used immediately upon isolation.



2

Compound **2** was prepared using the same procedure as compound **1** starting with compound **2a**:

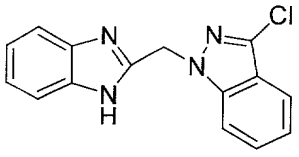
^{1}H NMR ($CDCl_3$) δ 2.24 (bs, 8 H), 2.57 (s, 3 H), 4.35 (t, J = 7.2 Hz, 2 H), 5.86 (s, 2 H), 7.09 (dt, J = 0.8, 7.9 Hz, 1 H), 7.24-7.32 (m, 4 H), 7.56 (d, J = 8.9 Hz, 1 H), 7.61 (d, J = 8.0 Hz, 1 H), 7.77-7.81 (m, 1 H);

IR (KBr, cm^{-1}) 3406, 2824, 1615, 1508, 1456, 1351, 1332, 744;

MS m/e 334 (MH^+);

Anal. Calcd for $C_{20}H_{23}N_5 \bullet 0.25\ H_2O$: C, 71.08; H, 7.01; N, 20.72

Found: C, 71.05; H, 7.06; N, 20.70.



3a

Compound **3a** was prepared using the same procedure as compound **1c** with 3-chloroindazole in 44% yield:

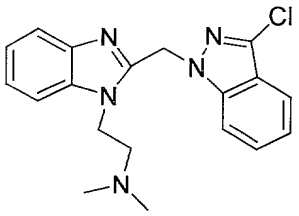
^{1}H NMR ($CDCl_3$) δ 5.79 (s, 2 H), 7.17-7.27 (m, 3 H), 7.40-7.60 (m, 1 H), 7.51-7.54 (m, 3 H), 7.66 (d, J = 8.2 Hz, 1 H);

IR (KBr, cm^{-1}) 2864, 2751, 1615, 1464, 1445, 1336, 1279, 1176, 989, 749.

MS m/e 283 (MH^+);

Anal. Calcd for $C_{15}H_{11}ClN_4$: C, 63.72; H, 3.92; N, 19.82

Found: C, 63.47; H, 3.98; N, 19.83.



3

Compound **3** was prepared using the same procedure as compound **1** in 63% yield:

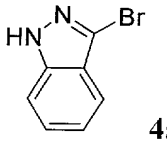
^1H NMR (CD_3OD) δ 2.28 (s, 6 H), 2.34 (t, J = 7.0 Hz, 2 H), 4.38 (t, J = 7.0 Hz, 2 H), 5.88 (s, 2 H), 7.15-7.25 (m, 1 H), 7.26-7.40 (m, 3 H), 7.62-7.68 (m, 3 H), 7.76-7.80 (m, 1 H);

IR (KBr, cm^{-1}) 2945, 2825, 2773, 1616, 1496, 1466, 1336, 1253, 1172, 1006, 992, 746;

MS m/e 353 (MH^+);

Anal. Calcd for $C_{19}H_{20}ClN_5$: C, 64.49; H, 5.70, N, 19.79

Found: C, 64.54; H, 5.72, N, 19.80.



4a

3-Bromoindazole **4a** was prepared using a procedure described by Boulton, B. E. and Coller, A. W (*Aust. J. Chem.*, **1974**, *27*, 2343-2346):

A solution of bromine (0.99 g, 6.19 mmol) in 10% NaOH was slowly added to a suspension of indazole (1 g, 8.50 mmol) in 2 N NaOH (25 mL). The reaction mixture became a thick white slurry. After stirring for 2 hours, a small

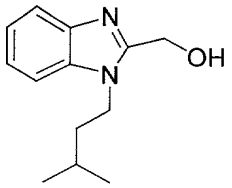
amount of sodium bisulfite was added and the solution was neutralized with 1 N HCl. The white solid was filtered and washed with water. Recrystallization from water gave 0.76 g (45% yield) of 3-bromoindazole **4a**:

^{1}H NMR ($CDCl_3$) δ 7.22-7.27 (m, 1 H), 7.43-7.52 (m, 2 H), 7.60-7.67 (m, 1 H); IR (KBr, cm^{-1}) 3154, 2944, 2915, 1624, 1479, 1331, 1242, 1026, 901, 770, 735, 639;

MS m/e 195 (MH^-);

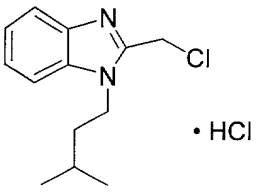
Anal. Calcd for $C_7H_5BrN_2$: C, 42.67; H, 2.56; N, 14.22

Found: C, 42.37; H, 2.55; N, 14.06.



4b

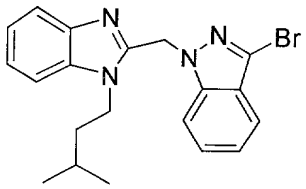
To a solution of 2-hydroxymethylbenzimidazole (27.1 g, 182.9 mmol) in a 1:1 mixture of DMF/THF (200 mL) was added NaH (60% in mineral oil, 8.05 g, 201.2 mmol) at room temperature. After stirring for 1.5 hour, 1-bromo-3-methylbutane (29 g, 192 mmol) was added and the mixture was stirred at 75 °C overnight. The mixture was adjusted to neutral pH with concentrated HCl and the solvent was evaporated. The residue was diluted with EtOAc, washed with water, dried over $MgSO_4$, and evaporated. The residue was crystallized from EtOAc/hexane to give 29 g of compound **4b** as white solid. The mother liquor was purified by flash chromatography (EtOAc:hexane = 1:1 to 2:1 and then EtOAc:MeOH = 10:0 to 10:1) to give additional 5.24 g (total 86% yield) of **4b**.



4c

To a solution of compound **4b** (34.24g, 156.9 mmol) in CH_2Cl_2 (100 mL) was slowly added $SOCl_2$ (28 g, 235.4 mmol) with ice-bath cooling. The resulting solution was stirred at room temperature for 1 hour and evaporated. The residue was dried *in vacuo* and then triturated with a mixture of CH_2Cl_2/Et_2O to give 41.25 g (96% yield) of compound **4c** as a white solid:

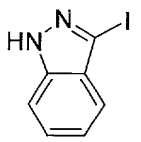
^{1}H NMR (DMSO-d_6) δ 0.99 (d, J = 6.3 Hz, 6 H), 1.72-1.79 (m, 3 H), 4.47-4.52 (m, 2 H), 5.36 (s, 2 H), 7.52-7.61 (m, 2 H), 7.82-7.92 (m, 2 H);
MS m/e 237 (MH^+).



4

To a solution of 3-bromoindazole (**4a** , 303 mg, 1.54 mmol) in CH_3CN (15 mL) was added NaH (60% suspension in mineral oil, 68 mg, 1.69 mmol). After stirring for 30 minutes at room temperature, compound **4c** was added and the reaction was stirred at room temperature for 22 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$ and evaporated. Purification of the resulting residue by column chromatography (hexanes / EtOAc, 1.5:1) followed by trituration with hexanes gave 191 mg (31% yield) of compound **4**:

^{1}H NMR ($CDCl_3$) δ: 0.91 (d, J = 6.6 Hz, 6 H), 1.11-1.18 (m, 1 H), 1.58-1.72 (m, 1 H), 4.20-4.26 (m, 2 H), 5.90 (s, 2 H), 7.16-7.21 (m, 1 H), 7.25-7.29 (m, 3 H), 7.34-7.39 (m, 1 H), 7.57 (dt, J = 1.0, 8.2, 1 H), 7.57 (d, J = 8.5, 1 H), 7.77-7.82 (m, 1 H);
IR (KBr, cm^{-1}) 2951, 1615, 1472, 1460, 1325, 1247, 1168, 973, 766, 738;
MS m/e 399 (MH^+);
Anal. Calcd for $C_{20}H_{21}BrN_4$: C, 60.46; H, 5.33; N, 14.10
Found: C, 60.30; H, 5.46; N, 14.05.



5a

3-iodoindazole (**5a**) was prepared using the same procedure as compound **4a** with iodine in 89% yield:

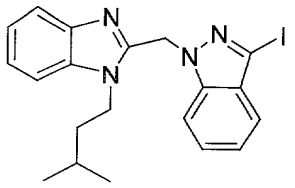
^{1}H NMR ($CDCl_3$) δ 7.21-7.27 (m, 1 H), 7.43-7.60 (m, 3 H);

IR (KBr, cm^{-1}) 3153, 2933, 2903, 1620, 1472, 1344, 1321, 1239, 1013, 899, 769, 747, 738;

MS m/e 243 (MH^-);

Anal. Calcd for $C_7H_5IN_2$: C, 34.45; H, 2.07; N, 11.45

Found: C, 34.62; H, 1.97; N, 11.38.



5

Compound **5** was prepared as an off-white solid using the same procedure as compound **4** with 3-iodoindazole (**5a**) in 54% yield:

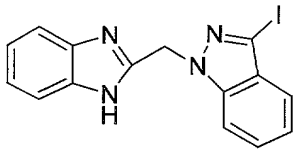
^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 6 H), 1.07-1.15 (m, 2 H), 1.60-1.66 (m, 1 H), 4.18-4.24 (m, 2 H), 5.94 (s, 2 H), 7.18 (t, J = 7.5 Hz, 1 H), 7.25-7.28 (m, 3 H), 7.37 (td, J = 7.7, 1.0 Hz, 1 H), 7.44 (d, J = 8.2 Hz, 1 H), 7.65 (d, J = 8.5 Hz, 1 H), 7.78-7.81 (m, 1 H);

IR (KBr, cm^{-1}) 2951, 1614, 1505, 1462, 1167, 967, 740;

MS m/e 445 (MH^+);

Anal. Calcd for $C_{20}H_{21}IN_4$: C, 54.06; H, 4.76; N, 12.61

Found: C, 53.90; H, 4.82; N, 12.35.



6a

Compound **6a** was prepared using the same procedure as compound **1c** with 3-iodoindazole (**5a)** in 34% yield:

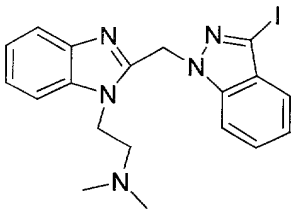
^{1}H NMR (DMSO-d_6) δ 5.92 (s, 2 H), 7.15-7.18 (m, 2 H), 7.27 (t, J = 4.7 Hz, 1 H), 7.46-7.53 (m, 4 H), 7.82 (d, J = 5.2 Hz, 1 H);

IR (KBr, cm^{-1}) 2830, 2625, 1613, 1538, 1490, 1457, 1445, 1276, 749;

MS m/e 375 (MH^+);

Anal. Calcd for $C_{15}H_{11}I \bullet 0.25H_2O$: C, 47.57; H, 3.06, N, 14.79

Found: C, 47.47; H, 2.93, N, 14.52.



6

Compound **6** was prepared as a yellow solid using the same procedure as compound **1** with compound **6a** and 2-chloro-N,N-dimethylethylamine hydrochloride in 51% yield:

^{1}H NMR ($CDCl_3$) δ 2.27 (s, 6 H), 2.31 (t, J = 7.2 Hz, 2 H), 4.36 (t, J = 7.0 Hz, 2 H), 5.96 (s, 2 H), 7.18-7.46 (m, 6 H), 7.67 (bd, J = 9.3 Hz, 1 H), 7.77-7.80 (m, 1 H);

IR (KBr, cm^{-1}) 3435, 1613, 1460, 1423, 1248, 1165, 740;

MS m/e 446 (MH^+);

Anal. Calcd for $C_{19}H_{20}IN_5$: C, 51.25; H, 4.53; N, 15.73

Found: C, 51.25; H, 4.51; N, 15.38.

The amine **6** and excess 4N HCl in dioxane were stirred in MeOH. The solvent was evaporated and the residue dried under vacuum to give the HCl salt of compound **6**:

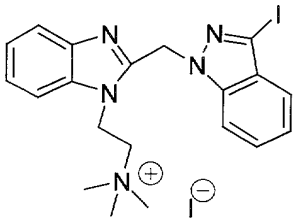
^{1}H NMR (CD_3OD) δ 3.13 (s, 6 H), 3.76-3.82 (m, 2 H), 5.17-5.23 (m, 2 H), 6.41 (s, 2 H), 7.35-7.40 (m, 1 H), 7.56-7.76 (m, 5 H), 7.92 (d, J = 8.5 Hz, 1 H), 8.09 (d, J = 7.9 Hz, 1 H);

IR (KBr, cm^{-1}) 3400, 2675, 1613, 1489, 1460, 1316, 1172, 970, 755;

MS m/e 446 (MH^+);

Anal. Calcd for $C_{19}H_{20}IN_5 \bullet 2HCl \bullet 0.5H_2O$: C, 43.28; H, 4.40, N, 13.28

Found: C, 43.22; H, 4.53, N, 13.17.



7

A mixture of the compound **6** (50 mg, 0.11 mmol) and methyl iodide (16 mg, 0.11 mmol) in acetone (1 mL) was stirred at room temperature for 17 hours. Collection of the solid by filtration gave 50 mg (77% yield) of compound **7** as a pale yellow solid:

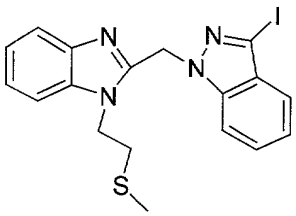
^{1}H NMR (CD_3OD) δ 3.32 (s, 9 H), 3.70-3.75 (m, 2 H), 5.01-5.07 (m, 2 H), 6.07 (s, 2 H), 7.27-7.59 (m, 5 H), 7.64 (d, J = 7.8 Hz, 1 H), 7.70 (d, J = 7.5 Hz, 1 H), 7.85 (d, J = 8.6 Hz, 1 H);

IR (KBr, cm^{-1}) 3435, 3011, 1615, 1489, 1475, 1459, 1414, 1248, 1168, 965, 755;

MS m/e 459 (M^+);

Anal. Calcd for $C_{20}H_{23}I_2N_5$: C, 40.91; H, 3.95; N, 11.93

Found: C, 40.87; H, 3.96; N, 11.65.



8

Compound **8** was prepared using the same procedure as compound **1** with compound **6a** and 2-chloroethyl methyl sulfide in 70% yield:

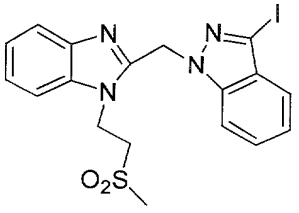
^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3 H), 2.63 (t, J = 7.1 Hz, 2 H), 4.61 (t, J = 7.1 Hz, 2 H), 6.14 (s, 2 H), 7.20 (t, J = 7.1 Hz, 1 H), 7.36-7.47 (m, 5 H), 7.84-7.89 (m, 2 H);

IR (KBr, cm^{-1}) 1613, 1460, 1426, 1331, 1163, 755, 743;

MS m/e 449 (MH^+);

Anal. Calcd for $C_{18}H_{17}IN_4S \bullet 0.25H_2O$: C, 47.74; H, 3.90; N, 12.37

Found: C, 47.64; H, 3.77; N, 12.23.



9

A mixture of compound **8** (75 mg, 0.17 mmol) and magnesium monoperoxyphthalate hexahydrate (MMPP, 165 mg, 0.33 mmol) in DMF (3 mL) was stirred at room temperature for 17 hours. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was separated, dried over $MgSO_4$, and evaporated. Column chromatography (EtOAc/hexanes, 2:1) gave compound **9**:

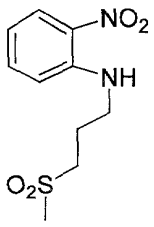
^{1}H NMR ($CDCl_3$) δ 2.97 (s, 3 H), 3.26 (bt, J = 7.6 Hz, 2 H), 4.88 (bt, J = 7.6 Hz, 2 H), 5.97 (s, 2 H), 6.92-7.51 (m, 6 H), 7.74-7.82 (m, 2 H);

IR (KBr, cm^{-1}) 1458, 1318, 1294, 1167, 1133, 966, 766, 742;

MS m/e 481 (MH^+);

Anal. Calcd for $C_{18}H_{17}IN_4O_2S \bullet 0.25H_2O$: C, 45.01; H, 3.57; N, 11.66

Found: C, 44.83; H, 3.58; N, 11.38.



10a

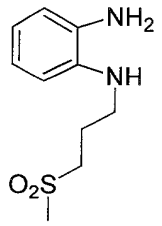
2-Fluoronitrobenzene (35.4 g, 250.9 mmol), 3-(methylthio)propylamine (24.0g, 228.1 mmol) and potassium carbonate (47.3 g, 342 mmol) were stirred in CH_3CN (100 mL) at room temperature for 18 hours. After stirring for an additional hour at reflux, the mixture was cooled to room temperature and filtered. The filtrate was evaporated. To the residue in DMF (150 mL), monoperoxyphthalic acid magnesium hexahydrate (168 g, 340 mmol) was added in several portions with ice-water cooling. The mixture was stirred at room temperature for 3 hours and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 and washed with 1 N NaOH, water, brine, dried over $MgSO_4$, and evaporated. The residue was triturated in hot EtOAc to give **10a** (48.7 g, 75% yield) as an orange solid:

^1H NMR ($CDCl_3$) δ 2.25-2.35 (m, 2 H), 2.97 (s, 3 H), 3.17 (t, J = 7.2 Hz, 2 H), 3.59 (t, J = 6.9 Hz, 2 H), 6.68-6.74 (m, 1 H), 6.89 (d, J = 8.1 Hz, 1 H), 7.45-7.51 (m, 1 H), 8.20 (dd, J = 1.5, 8.7 Hz, 1 H);

MS m/e 259 (MH^+);

Anal. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.50; H, 5.46; N, 10.84

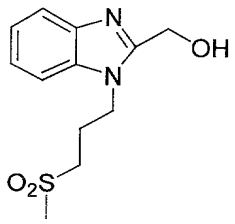
Found: C, 46.53; H, 5.54; N, 10.90.



10b

To a suspension of **10a** (48.5 g, 187.8 mmol) in a mixture of $CHCl_3$ and MeOH (150 mL,1:3) was added 10% palladium on carbon (6 g) under nitrogen. The reduction was carried out in a Parr shaker with hydrogen pressure maintained between 40 and 60 psi for 25 min. The catalyst was removed by filtration and the filtrate was evaporated to give crude **10b**:

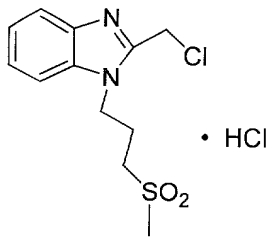
^{1}H NMR (CD_3OD) δ 2.11-2.21 (m, 2 H), 2.98 (s, 3 H), 3.28-3.36 (m, 4 H), 6.75 (dt, J = 0.9, 7.2 Hz, 1 H), 6.85 (d, J = 7.5 Hz, 1 H), 7.06-7.12 (m, 2 H); MS m/e 229 (MH^+).



10c

Diamine **10b** was stirred at reflux for 18 hours with glycolic acid (15.7 g, 207 mmol) in 6 N HCl (150 mL). The solution was cooled in an ice bath and neutralized with concentrated NH_4OH solution, extracted with EtOAc, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography (gradient, EtOAc: hexane =1:1, EtOAc, then EtOAc:MeOH = 10:1) to give a product which crystallized from EtOAc/MeOH to afford 25.7 g (51% yield over two steps) of compound **10c**:

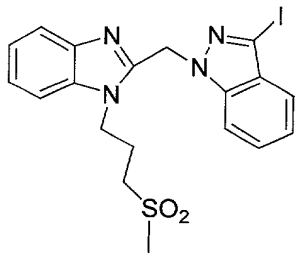
^{1}H NMR (CD_3OD) δ 2.38-2.44 (m, 2 H), 2.97 (s, 3 H), 3.24 (t, J = 7.6 Hz, 2 H), 4.54 (t, J = 7.6 Hz, 2 H), 7.27 (t, J = 1.1, 8.1 Hz, 1 H), 7.33 (dt, J = 1.1, 8.0 Hz, 1 H), 7.62 (d, J = 8.1 Hz, 1 H), 7.64 (dd, J = 1.0, 8.0 Hz, 1 H);
MS m/e 269 (MH^+).



10d

Compound **10d** was prepared using the same procedure as compound **4c** with alcohol **10c**:

^{1}H NMR (CD_3OD) δ 2.46-2.52 (m, 2 H), 3.03 (s, 3 H), 3.37 (t, J = 7.1 Hz, 2 H), 4.77 (t, J = 7.8 Hz, 2 H), 5.31 (s, 2 H), 7.68-7.73 (m, 2 H), 7.86 (dd, J = 2.8, 6.9 Hz, 1 H), 8.03 (dd, J = 1.7, 6.1 Hz, 1 H);
MS m/e 287 (MH^+).

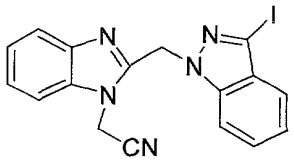


10

Compound **10** was prepared using the same procedure as compound **4** with compound **5a** and compound **10d**:

^{1}H NMR ($CDCl_3$) δ 1.88-2.00 (m, 2 H), 2.85 (s, 3 H), 3.05-3.10 (m, 2 H), 4.76-4.81 (m, 2 H), 6.35 (s, 2 H), 7.08-7.27 (m, 1 H), 7.25 (d, J = 8.4 Hz, 1 H), 7.37-7.44 (m, 3 H), 7.54-7.57 (m, 1 H), 7.77-7.80 (m, 1 H), 8.34 (d, J = 8.7 Hz, 1 H);

MS m/e 495 (MH^+).

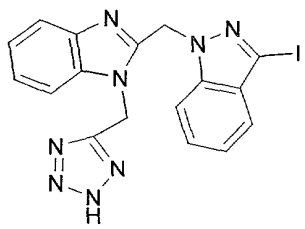


11

Compound **11** was prepared using the same procedure as compound **1** with compound **6a** and bromoacetonitrile in 42% yield:

^{1}H NMR ($CDCl_3$) δ 5.42 (s, 2 H), 5.93 (s, 2 H), 7.19-7.47 (6 H), 7.67 (d, J = 8.7 Hz, 1 H), 7.79 (dd, J = 2.1, 6.6 Hz, 1 H);

IR (KBr, cm^{-1}) 3435, 1615, 1464, 1412, 1198, 752, 741.



12

A mixture of compound **11** (310 mg, 0.75 mmol), sodium azide (146 mg, 2.25 mmol), and ammonium chloride (120 mg, 2.25 mmol) in DMF (15 mL) was stirred at 110 °C for 16 hours. The solid was filtered and the filtrate was evaporated under vacuum. The residue was dissolved in 1N NaOH and the aqueous solution was washed with EtOAc. The aqueous solution was adjusted to pH 7 and then extracted with EtOAc. The organic extracts were dried over $MgSO_4$ and evaporated to give 260 mg of crude product which was converted to sodium salt by adding 1N NaOH (0.54 mL, 0.54 mmol) in MeOH (5 mL). The solvent was evaporated and the residue was purified by C18 column chromatography to give 40 mg of compound **12** as the sodium salt:

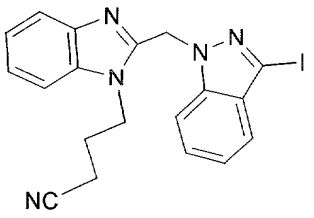
^{1}H NMR (CD_3OD) δ 5.84 (s, 2 H), 6.19 (s, 2 H), 7.20-7.30 (m, 3 H), 7.47-7.60 (m, 4 H), 7.70 (d, J = 8.9 Hz, 1 H);

IR (KBr, cm^{-1}) 3368, 1615, 1462, 1321, 1247, 1168, 741;

MS m/e 457 (MH^+);

Anal. Calcd for $C_{17}H_{13}IN_8Na \bullet 1.75\ H_2O$: C, 40.06; H, 3.06; N, 21.98

Found: C, 40.30; H, 3.33; N, 21.66.



13

Compound **13** was prepared using the same procedure as compound **1** with compound **6a** and 4-bromobutyronitrile:

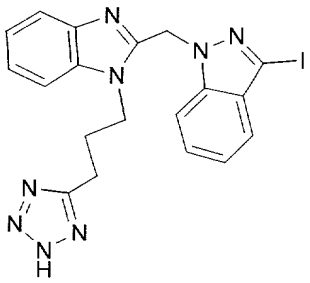
^1H NMR ($CDCl_3$) δ 1.59-1.69 (m, 2 H), 2.38 (t, J = 7.0 Hz, 2 H), 4.45 (t, J = 8.7 Hz, 2 H), 5.94 (s, 2 H), 7.20-7.48 (m, 6 H), 7.72 (d, J = 8.5 Hz, 1 H), 7.79-7.84 (m, 1 H);

IR (KBr, cm^{-1}) 3424, 2943, 1614, 1459, 1418, 1166, 742;

MS m/e 442 (MH^+);

Anal. Calcd for $C_{19}H_{16}IN_5$: C, 51.72; H, 3.65; N, 15.87

Found: C, 51.63; H, 3.87; N, 15.61.



14

Compound **14** was prepared using the same procedure as compound **12** with compound **13**:

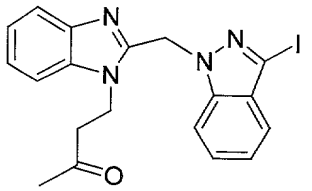
^{1}H NMR (CD_3OD) δ 1.94-2.03 (m, 2 H), 2.85 (t, J = 7.2 Hz, 2 H), 4.37 (t, J = 7.7 Hz, 2 H), 5.98 (s, 2 H), 7.23-7.32 (m, 3 H)), 7.39-7.52 (m, 3 H), 7.60-7.69 (m, 2 H);

IR (KBr, cm^{-1}) 3395, 1615, 1459, 1327, 1167, 743;

MS m/e 485 (MH^+);

Anal. Calcd for $C_{19}H_{16}IN_8Na \bullet 3.00\ H_2O$: C, 41.05; H, 4.08; N, 19.54

Found: C, 41.03; H, 3.87; N, 19.24.



15

Compound **6a** (800 mg, 2.14 mmol) and methyl vinyl ketone (600 mg, 8.55 mmol) were refluxed in EtOH (25 mL) for 18 hours. The solvent was evaporated to give a tan solid. This solid was triturated with Et_2O and filtered to give 825 mg (87% yield) of compound **15**:

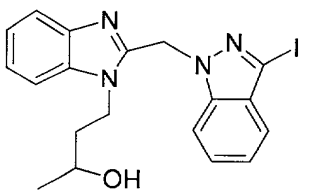
^{1}H NMR ($CDCl_3$) δ 2.09 (s, 3 H), 2.58 (t, J = 7.1 Hz, 2 H), 4.59 (t, J = 7.1 Hz, 2 H), 6.03 (s, 2 H), 7.20-7.30 (m, 4 H), 7.41-7.48 (m, 2 H), 7.77-7.81 (m, 2 H);

IR (KBr, cm^{-1}) 3396, 1702, 1614, 1420, 1461, 1368, 1323, 1247, 1166, 1151, 742;

MS m/e 445 (MH^+);

Anal. Calcd for $C_{19}H_{17}IN_4O$: C, 51.37; H, 3.86; N, 12.61

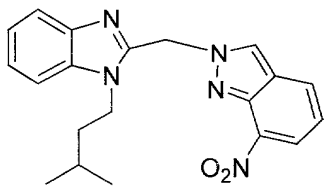
Found: C, 51.48; H, 3.91; N, 12.50.



16

Ketone **15** (300 mg, 0.68 mmol) was suspended in MeOH (10 mL) and cooled to 0 °C with an ice bath. Sodium borohydride (25 mg, 0.68 mmol) was added and the reaction mixture was allowed to stir while warming to room temperatature. The solvent was evaporated. The residue was diluted with water and extracted with Et_2O. The organic extracts were dried over $MgSO_4$ and evaporated. Trituration with Et_2O followed by filtration gave 210 mg (70% yield) of compound **16**:

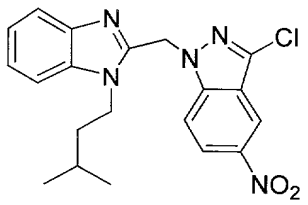
^{1}H NMR ($CDCl_3$) δ 1.18 (d, J = 6.2 Hz, 3 H), 1.52-1.56 (m, 2 H), 3.78-3.82 (m, 1 H), 4.12-4.53 (m, 2 H), 5.99 (q, J = 15.2 Hz, 2 H), 7.21 (t, J = 7.6 Hz, 1 H), 7.27-7.30 (m, 1 H), 7.37-7.39 (m, 1 H), 7.42-7.46 (m, 2 H), 7.77-7.81 (m, 2 H);
IR (KBr, cm^{-1}) 3392, 2960, 2925, 1614, 1461, 1421, 1323, 1248, 1165, 742;
MS m/e 447 (MH^+);
Anal. Calcd for $C_{19}H_{19}IN_4O$: C, 51.13; H, 4.29; N, 12.55
Found: C, 50.93; H, 4.22; N, 12.27.



17

Compound **17** was prepared using the same procedure as compound **4** with 7-nitroindazole in 20% yield:

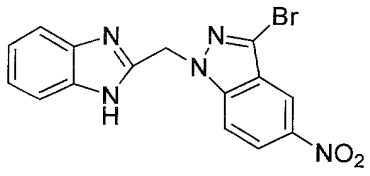
^{1}H NMR ($CDCl_3$) δ 0.82 (d, J = 6.6 Hz, 6 H), 1.25-1.40 (m, 2 H), 1.53-1.68 (m, 1 H), 4.27-4.32 (m, 2 H), 6.00 (s, 2 H), 7.12 (t, J = 7.9 Hz, 1 H), 7.19-7.30 (m, 3 H), 7.69-7.73 (m, 1 H), 7.92 (dd, J = 0.8, 8.3 Hz, 1 H), 8.28 (dd, J = 0.9, 7.6 Hz, 1 H), 8.31 (s, 1 H);
IR (KBr, cm^{-1}) 2957, 1728, 1516, 1455, 1407, 1335, 1301, 1138, 737;
MS m/e 364 (MH^+).



18

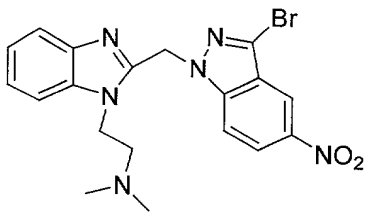
Compound **18** was prepared using the same procedure as compound **4** with 3-chloro-5-nitroindazole in 33% yield:

^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 6 H), 1.18-1.28 (m, 2 H), 1.58-1.71 (m, 1 H), 4.19-4.25 (m, 2 H), 5.82 (s, 2H), 7.19-7.25 (m, 3 H), 7.69-7.72 (m, 1 H), 7.79 (d, J = 9.3 Hz, 1 H), 8.19 (dd, J = 2.1, 9.3 Hz, 1 H), 8.57 (d, J = 2.1, 1 H);
IR (KBr, cm^{-1}) 2956, 1586, 1616, 1524, 1459, 1339, 794, 749;
MS m/e 398 (MH^+);
Anal. Calcd for $C_{20}H_{20}N_5O_2Cl$: C, 60.38; H, 5.07; N, 17.60
Found: C, 60.67; H, 5.42; N, 17.03.



19a

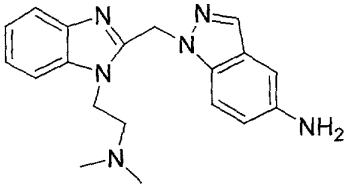
Compound **19a** was prepared using the same procedures as compound **1c** with 3-bromo-5-nitroindazole and was used without further purification.



19

Compound **19** was prepared using the same procedures as compound **1** with compound **19a** and 2-chloro-N,N-dimethylethylamine hydrochloride in 25% yield:

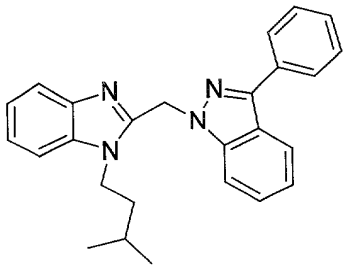
^{1}H NMR ($CDCl_3$) δ 2.32 (s, 6 H), 2.49 (bt, 2 H), 4.42 (bt, 2 H), 5.97 (s, 2 H), 7.28-7.33 (m, 3 H), 7.75-7.79 (m, 1 H), 7.88 (d, J = 9.3 Hz, 1 H), 8.27 (dd, J = 2.1, 9.3 Hz, 1 H), 8.57 (d, J = 2.1 Hz, 1 H);
IR (KBr, cm^{-1}) 2943, 2772, 1616, 1517, 1456, 1340, 1277, 737;
MS m/e 443 (MH^+);
Anal. Calcd for $C_{19}H_{21}BrN_6O_2$: C, 51.25; H, 4.75, N, 18.87
Found: C, 51.38; H, 4.45, N, 18.88.



20

Compound **19** (40 mg, 0.09 mmol) was reduced in a Parr apparatus under H_2 in the presence of 10% palladium on carbon (40 mg) in a mixture of MeOH and $CHCl_3$ (2.4 mL, 5:1) for 2 hours at 35 psi. The catalyst was removed by filtration through a pad of celite and the filtrate was evaporated to give compound **20**:

^{1}H NMR ($CDCl_3$) δ 3.12 (s, 6 H), 3.57-3.65 (m, 2 H), 5.00-5.06 (m, 2 H), 6.19 (s, 2 H), 7.35-7.49 (m, 2 H), 7.67 (d, J = 7.8 Hz, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.87 (s, 1 H), 8.06 (d, J = 8.9 Hz, 1 H), 8.29 (s, 1 H);
MS m/e 335 (MH^+).



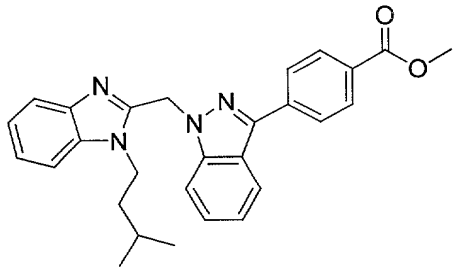
21

A mixture of compound **4** (40 mg, 0.10 mmol), phenyltrimethyltin (29 mg, 0.12 mmol), and palladium tetrakistriphenylphosphine (12 mg, 0.01 mmol) in toluene (2 ml) was heated to reflux for 3 hours. The reaction mixture was diluted with EtOAc (10 ml), washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residue was purified by prep-HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 34 mg (86% yield) of compound **21** as a pale yellow solid:

^1H NMR (CD_3OD) δ 0.77 (d, J = 6.6 Hz, 6 H), 1.30-1.40 (m, 2 H), 1.40-1.56 (m, 1 H), 4.45-4.50 (m, 2 H), 6.26 (s, 2 H), 7.32-7.58 (m, 8 H), 7.75 (m, 3 H), 7.91 (d, J = 6.9 Hz, 1 H), 8.07 (d, J = 8.1 Hz, 1 H);

IR (KBr, cm^{-1}) 2960, 1683, 1492, 1188, 1136, 749;

MS m/e 395 (MH^+).

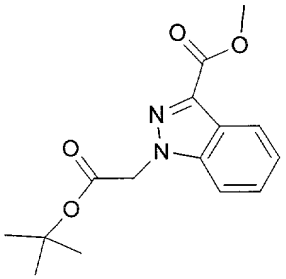


22

Compound **22** was prepared using the same procedure as compound **21** with 4-trimethylstannyl-benzoic acid methyl ester prepared according to the procedure described by Wursthorn, K.R. and Kuivila, H.G. (*J. Organomet. Chem.*, **1977**, *140 (1)*, 29-39):

^{1}H NMR ($CDCl_3$) δ 0.82 (d, J = 6.6 Hz, 6H), 1.18-1.25 (m, 2 H), 1.71-1.79 (m, 1 H), 3.97 (s, 3 H), 4.21-4.38 (m, 2 H), 6.00 (s, 2 H), 7.25-7.42 (m, 6 H), 7.71-7.84 (m, 2 H), 8.02-8.21 (m, 4 H);

MS m/e 453 (MH^+).



23a

A solution of indazole-3-carboxylic acid (Fluka, 3.0 g, 18.5 mmol) in MeOH (50 ml) with concentrated sulfuric acid (0.1 ml) was heated to reflux for 12 hours, cooled and concentrated. The residue was dissolved in EtOAc and washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to give 2.32 g (70% yield) of the methyl ester as a dark solid. The ester was dissolved in CH_3CN (50 mL), treated with K_2CO_3 (0.83 g, 6.0 mmol) and t-butyl bromoacetate (0.84 mL, 5.7 mmol), and stirred at room temperature for 12 hours. The solution was filtered and concentrated. The residue was purified by flash chromatography (gradient, hexanes:EtOAc = 20:1 to 5:1) to give 1.44 g (87% yield) of compound **23a**:

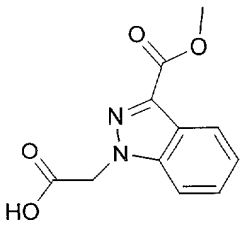
^{1}H NMR (DMSO-d_6) δ 1.41 (s, 9 H), 3.93 (s, 3 H), 5.44 (s, 2 H), 7.36 (t, J = 7.1 Hz, 1 H), 7.51 (J = 7.2 Hz, 1 H), 7.78 (d, J = 8.1 Hz, 1 H), 8.08 (d, J = 8.1Hz, 1 H);

IR (KBr, cm^{-1}) 2986, 1746, 1720, 1230;

MS m/e 290 (MH^+);

Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65

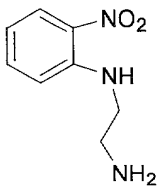
Found: C, 62.23; H, 6.27; N, 9.63.



23b

Compound **23a** (1.2 g, 4.13 mmol) was dissolved in TFA (5 mL) and stirred for 12 hours. The solution was concentrated to give 0.96 g (99% yield) of compound **23b**:

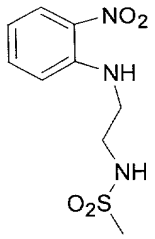
^{1}H NMR (DMSO-d_6) δ 3.93 (s, 3 H), 5.44 (s, 2 H), 7.36 (t, J = 7.1 Hz, 1 H), 7.50 (t, J = 7.1 Hz, 1 H), 7.80 (d, J = 8.2 Hz, 1 H), 8.09 (d, J = 8.2 Hz, 1 H);
IR (KBr, cm^{-1}) 1716, 1323, 1149, 747;
MS m/e 234 (MH^+).



23c

A solution of 2-fluoronitrobenzene (30 mL, 2.84 mmol) in CH_3CN (30 mL) was added to a solution of ethylenediamine (76 mL, 1.14 mmol) in CH_3CN (50 mL). The mixture was stirred at room temperature for 12 hours then concentrated to give 51 g (99% yield) of the product **23c** as an orange oil:

^{1}H NMR (DMSO-d_6) δ 2.82 (t, J = 6.0 Hz, 2 H), 3.30 (t, J = 6.0 Hz, 2 H), 6.66 (t, J = 8.4 Hz, 1 H), 7.05 (d, J = 8.7 Hz, 1 H), 7.53 (d, J = 8.4 Hz, 1 H), 8.30-8.34 (m, 1 H);
IR (film, cm^{-1}) 1621, 1514, 1347, 740;
MS m/e 182 (MH^+);
Anal. Calcd for $C_8H_{11}N_3O_2 \cdot 0.20\ H_2O$: C, 51.99; H, 6.22; N, 22.74
Found: C, 51.99; H, 6.29; N, 22.46.



23d

To a mixture of amine **23c** (2.0 g, 11 mmol) in CH_2Cl_2 (50 mL) was added triethyl amine (1.53 mL, 11 mol) and the mixture was cooled to 0°C. Methanesulfonyl chloride (0.85 mL, 11 mmol) was added slowly. Once the addition was complete the reaction mixture was warmed to room temperature and stirred for 12 hours. The mixture was poured into water and the aqueous layer separated, dried over MgSO4, and evaporated. The residue was chromatographed (3% MeOH in CH_2Cl_2) to give 2.55 g (89% yield) of **23d** as an orange oil:

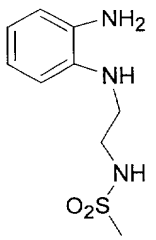
^{1}H NMR (DMSO-d_6) δ 2.91 (s, 3 H), 3.18 (dd, J = 6.1, 11.6 Hz, 2 H), 3.39-3.42 (m, 2 H), 6.70 (t, J = 9.0 Hz, 1 H), 7.08 (d, J = 8.5 Hz, 1 H), 7.28 (t, J = 6.1 Hz, exchanges with D_2O, 1 H), 7.55 (td, J = 1.0, 6.0, Hz, 1 H); 8.07 (dd, J = 1.0, 8.7 Hz, 1 H); 8.23 (bs, 1H exchanges with D_2O);

IR (film, cm^{-1}) 1511, 1354, 1317, 1151;

MS m/e 260 (MH^+);

Anal. Calcd for $C_9H_{13}N_3O_4S$•0.5 H_2O•0.08 EtOAc: C, 40.66; H, 5.36; N, 15.26

Found: C, 40.58; H, 5.29; N, 14.88.

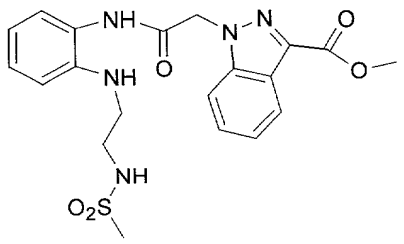


23e

A mixture of compound **23d** (1.0 g, 3.9 mmol) and 10% palladium on carbon (100 mg) in EtOH (50 mL) was hydrogenated at 50 psi for 12 hours. The

mixture was filtered and the filtrate was evaporated to give an orange oil. The residue was chromatographed (1% MeOH in CH_2Cl_2) to give 0.55g (62% yield) of compound **23e** as a dark oil:

^{1}H NMR (DMSO-d_6) δ 2.91 (s, 3 H), 3.17 (bs, 2 H), 4.45 (bs, 3 H, 1H exchanges with D_2O), 6.40-6.56 (m, 4 H), 7.11 (bs, 1 H, exchanges with D_2O);
IR (film, cm^{-1}) 3326, 1625, 1510, 1315, 1148, 738;
MS m/e 230 (MH^+);
Anal. Calcd for $C_9H_{15}N_3O_2S$: C, 46.78; H, 6.63; N, 18.18
Found: C, 46.81; H, 6.79; N, 17.81.



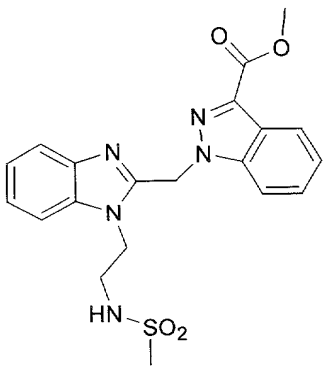
23f

Compound **23b** (0.4 g, 1.7 mmol) and thionyl chloride (5 mL) were stirred at reflux for 30 minutes. The excess thionyl chloride was evaporated *in vacuo* to give the corresponding acid chloride. Diamine **23e** was dissolved in CH_2Cl_2 (10 mL), treated with Et_3N (0.21 g, 2.0 mmol) and cooled to -78°C. A solution of the acid chloride in CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was stirred at -78°C for 1 hour, then warmed to room temperature and stirred for 12 hours. The precipitate was filtered to give 0.33 g (44% yield) of compound **23f**:

^{1}H NMR (DMSO-d_6) δ 2.91 (s, 3 H), 3.13-3.17 (m, 2 H), 3.21-3.32 (m, 2 H), 3.93 (s, 3 H), 5.26 (t, J = 5.6 Hz, 1 H, exchanges with D_2O), 5.49 (s, 2 H), 6.57 (t, J = 7.6 Hz, 1 H), 6.68 (d, J = 8.0, 1 H), 7.02-7.18 (m, 4 H, 1 H exchanges with D_2O), 7.36 (t, J = 7.7 Hz, 1 H), 7.52 (t, J = 7.8 Hz, 1 H), 7.80 (d, J = 8.5 Hz, 1 H), 8.09 (d, J = 8.2 Hz, 1 H), 9.57 (s, 1 H, exchanges with D_2O);
IR (KBr, cm^{-1}) 1730, 1681, 1541, 1311, 1169;
MS m/e 445 (MH^+);

Anal. Calcd for $C_{20}H_{23}N_5O_5S$: C, 53.92; H, 5.20; N, 15.72

Found: C,53.57 ; H, 5.22; N, 15.58.



23

Compound **23f** was dissolved in AcOH (20 mL) and heated to reflux for 4 hours. The mixture was cooled and concentrated. The residue was purified by flash chromatography (gradient, MeOH/CH_2Cl_2, 3% to 5%) to give 240 mg (85% yield) of compound **23** as a white foam:

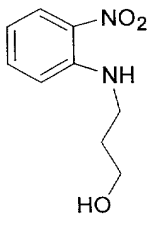
^{1}H NMR (DMSO-d_6) δ 2.83 (s, 3 H), 3.34-3.39 (m, 2 H), 4.48-4.52 (m, 2 H), 6.21 (s, 2 H), 7.16 (t, J = 7.9 Hz, 1 H), 7.26 (t, J = 7.2 Hz, 1 H), 7.35-7.45 (m, 2 H), 7.48-7.53 (m, 2 H), 7.61 (d, J = 8.0 Hz, 1 H), 8.11 (d, J = 8.2 Hz, 1 H), 11.97 (s, 1 H, exchanges with D_2O);

IR (KBr, cm^{-1}) 1716, 1323, 1149, 747;

MS m/e 427 (MH^+);

Anal. Calcd for $C_{20}H_{21}N_5O_4 \bullet 0.35\ H_2O \bullet 0.53$ AcOH: C, 54.33; H, 5.16; N, 15.04

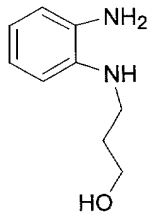
Found: C, 54.33; H, 5.16; N, 15.16.



24a

A solution of 2-fluoronitrobenzene (5.0 g, 35.5 mmol) and 1-amino-3-propanol (2.65 g, 35.5 mmol) in CH_3CN (100 mL) and triethylamine (4.1 g, 40 mmol) was heated to reflux for 12 hours, then cooled and concentrated. The residue was dissolved in EtOAc and washed with 1N HCl. The organic layer was dried over $MgSO_4$ and concentrated to give 6.5 g (93% yield) of compound **24a** as a dark orange solid:

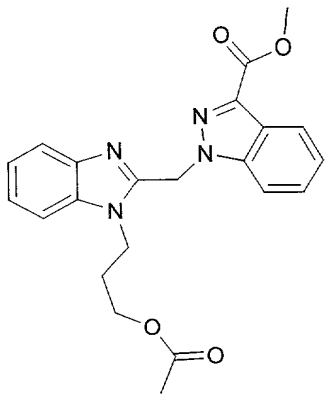
^{1}H NMR (DMSO-d_6) δ 1.95-2.10 (m, 2 H), 3.48 (t, J = 6.7 Hz, 2 H), 3.86 (t, J = 6.7 Hz, 2 H), 6.61-6.67 (m, 1 H), 6.90 (d, J = 9 Hz, 1 H), 7.41-7.47 (m, 1 H), 8.17 (d, J = 7.8 Hz, 1 H);
IR (KBr cm^{-1}) 3378, 1512, 1353, 1069;
MS m/e 196 (MH^+).



24b

A solution of compound **24a** (6.5 g, 33.1 mmol) in EtOH (50 mL) was hydrogenated at 40 psi with 10% palladium on carbon (100 mg) for 4 hours. The catalyst was removed by filtration and the filtrate was evaporated to give 2.7 g (38% yield) of compound **24b** as a dark oil:

^{1}H NMR(DMSO-d_6) δ 1.90-1.94 (m, 2 H), 3.27 (t, J = 6.4 Hz, 2 H), 3.83 (t, J = 5.9 Hz, 2 H), 6.67-6.73 (m, 3 H) 6.81-6.85 (m, 1 H);
MS m/e 166 (MH^+).



24

Compound **24** was prepared using the same sequence as compound **23** with compound **23b** and compound **24b**:

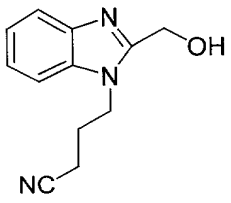
^{1}H NMR (DMSO-d_6) δ 1.86-1.98 (m, 2 H), 1.99 (s, 3 H), 3.91 (s, 3 H), 3.98 (t, J = 6.2 Hz, 2 H), 4.42 (t, J = 7.4 Hz, 2 H), 6.18 (s, 2 H), 7.15-7.28 (m, 2 H), 7.38 (t, J = 7.5 Hz, 1 H), 7.50-7.58 (m, 2 H), 7.90 (d, J = 8.5 Hz, 1 H), 8.10 (d, J = 8.1 Hz, 1 H);

IR (KBr, cm^{-1}) 1740, 1723, 740;

MS m/e 406 (MH^+);

Anal. Calcd for $C_{22}H_{22}N_4O_4$: C, 65.01; H, 5.46; N, 13.78

Found: C, 64.87; H, 5.56; N, 13.66.

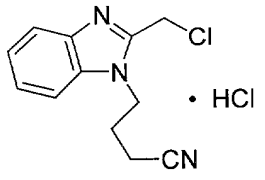


25a

To a solution of 2-hydroxymethylbenzimidazole (29.63 g, 200 mmol) in a mixture of DMF/THF (150 mL, 1:1) was added sodium hydride (60% in mineral oil, 8.4 g, 210 mmol) in several portions at room temperature. After stirring for 1 hour, 4-bromobutyronitrile (29.6 g, 200 mmol) was added and the resulting solution was stirred at 80 °C for 18 hours. The solvent was evaporated. The

residue was diluted with H_2O and extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (EtOAc: hexane = 1:1 to 2:1, then EtOAc: MeOH =10:1) to give 22.11 g (51% yield) of **25a** as a white solid:

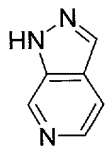
^{1}H NMR ($CDCl_3$) δ 2.27-2.32 (m, 2 H), 2.41 (t, J = 6.0 Hz, 2 H), 4.41 (t, J = 7.2 Hz, 2 H), 7.26-7.38 (m, 3 H), 7.67-7.70 (m, 1 H);
MS m/e 216 (MH^+).



25b

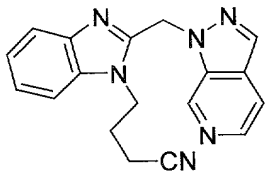
To alcohol **25a** (22 g, 102.2 mmol) suspended in CH_2Cl_2 (100 mL) was slowly added thionyl chloride (15.81 g, 132.9 mmol) while cooling at 0 °C with an ice bath. The ice bath was removed and the solution was stirred at room temperature for 1 hour. The solvent was evaporated. The residue was triturated with EtOAc to give a nearly quantitative yield of **25b** as light gray powder:

^{1}H NMR ($CDCl_3$) δ 2.32-2.38 (m, 2 H), 2.70 (t, J = 7.3 Hz, 2 H), 4.69 (t, J = 7.6 Hz, 2 H), 5.33 (s, 2 H), 7.69-7.74 (m, 2 H), 7.85-7.87 (m, 1 H), 8.00-8.02 (m, 1 H);
MS m/e 234 (MH^+);
Anal. Calcd for $C_{12}H_{12}N_3$•HCl•0.25 H_2O: C, 52.48; H, 4.95; N, 15.30
Found: C, 52.52; H, 4.88; N, 15.26.



25c

1H-pyrazolo[3,4-c]pyridine **25c** was prepared according to the procedure described by D. Chapman et al. (*Journal of the Chemical Society, Perkin Transactions I,* **1980**, 2398).

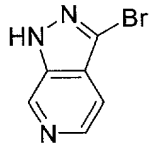


25

A suspension of 1H-pyrazolo[3,4-c]pyridine (**25c**, 24 mg, 0.20 mmol) and Cs_2CO_3 (196 mg, 0.60 mmol) in DMF (4 ml) was pre-mixed for 2 hours before compound **25b** (54 mg, 0.20 mmol) was added to the mixture. The reaction mixture was stirred at room temperature for 18 hours. The mixture was diluted with EtOAc (10 ml), washed with H_2O and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by preperative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to yield 35 mg (55% yield) of compound **25** as a viscous oil:

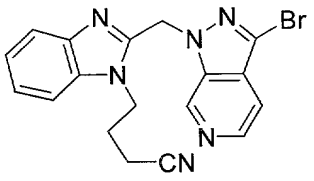
^{1}H NMR (CD_3OD) δ 2.20-2.26 (m, 2H), 2.64 (t, J=7.2 Hz, 2H), 4.68 (t, J=7.6 Hz, 2H), 6.44 (s, 2H), 7.39-7.42 (m, 1H), 7.46-7.49 (m, 1H), 7.65 (d, J=8.1 Hz, 1H), 7.75 (d, J=8.2 Hz, 1H), 8.38 (d, J=6.2 Hz, 1H), 8.47 (d, J=6.2 Hz, 1H), 8.64 (s, 1H), 9.77 (s, 1H);

MS m/e 317 (MH^+).



26a

3-Bromo-1H-pyrazolo[3,4-c]pyridine **26a** was prepared the procedure described by D. Chapman et al. (*Journal of the Chemical Society, Perkin Transactions I*, **1980**, 2398).

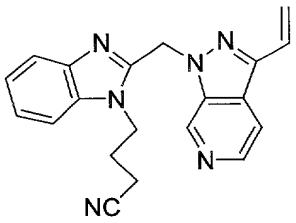


26

Compound **26** was prepared using the same procedure as compound **25** with compound **25b** and compound **26a**:

^{1}H NMR ($CDCl_3$) δ 1.83-1.89 (m, 2H), 2.42 (t, J=7.0 Hz, 2H), 4.47 (t, J=7.6 Hz, 2H), 5.97 (s, 2H), 7.28-7.37 (m, 3H), 7.48-7.49 (m, 1H), 7.78-7.79 (m, 1H), 8.39 (d, J=5.6 Hz, 1H), 9.29 (d, J=0.4 Hz, 1H);

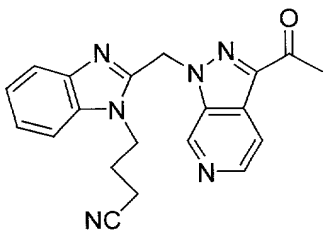
MS m/e 394, 396 (MH^+).



Compound **27** was prepared using the same procedure as Compound **21** starting with compound **26** and tributylvinyltin.

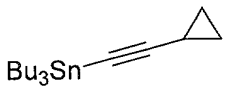
^{1}H NMR ($CDCl_3$) δ 1.73-1.79 (m, 2H), 2.33 (t, J=7.0 Hz, 2H), 4.45 (t, J=7.6 Hz, 2H), 5.63 (d, J=11.4 Hz, 1H), 5.99 (s, 2H), 6.14 (d, J=18 Hz, 1H), 6.99-7.04 (m, 1H), 7.29-7.34 (m, 3H), 7.75 (d, J=5.6 Hz, 1H), 7.80-7.82 (m, 1H), 8.37 (d, J=5.6 Hz, 1H), 9.27 (s, 1H);

MS m/e 343 (MH^+).



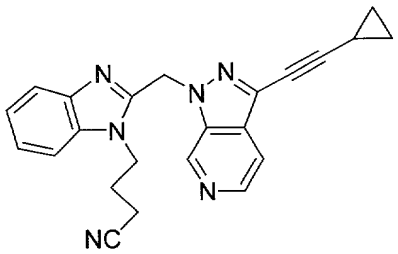
Compound **28** was prepared using the same procedure as compound **21** starting with compound **26** and tributyl(1-ethoxyvinyl)tin. The crude product formed was stirred in 25% HCl-MeOH for 2 h and purified by preparative-HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give the desired product (78%).

^{1}H NMR (CD_3OD) δ 2.31-2.38 (m, 2H), 2.69-2.73 (m, 5H), 4.76 (t, J=7.5 Hz, 2H), 6.59 (s, 2H), 7.44-7.48 (m, 1H), 7.52-7.55 (m, 1H), 7.66-7.69 (m, 1H), 7.83-7.85 (m, 1H), 8.61-8.65 (m, 2H), 9.80 (s, 1H);
MS m/e 359 (MH^+).



29a

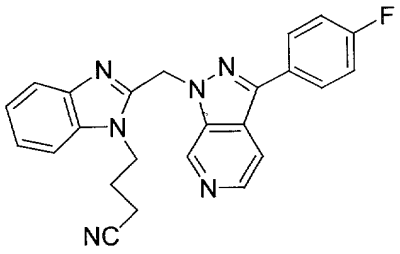
To a solution of 5-chloropentyne (2.05 g, 20.0 mmol) in THF (20 ml) at –28^{0}C was added butyllithium (2.5 M in hexane, 16.4 ml, 41.0 mmol) dropwise. The formed solution was kept at 0^{0}C for 1h before addition of tributyltin chloride (6.44 g, 19.8 mmol). The final solution was heated to reflux for 2 h, cooled down to the ambient temperature, diluted with EtOAc (200 ml). The organic layer was washed with aqueous $NaHCO_3$ saturated aqueous NaCl respectively, dried over $MgSO_4$, concentrated and was used as crude without further purification.



Compound **29** was prepared using the same procedure as compound **21** starting with compound **26** and tributyl-cyclopropylethynyl-stannane.

^{1}H NMR (CD_3OD) δ 0.88-0.90 (m, 2H), 0.98-1.02 (m, 2H), 1.60-1.65 (m, 1H), 2.19-2.25 (m, 2H), 2.66 (t, J=7.2 Hz, 2H), 4.68 (t, J=7.5 Hz, 2H), 6.38 (s, 2H), 7.42-7.45 (m, 1H), 7.48-7.51 (m, 1H), 7.66 (d, J=8.1 Hz, 1H), 7.78 (d, J=8.2 Hz, 1H), 8.18-8.19 (m, 1H), 8.47 (d, J=6.0 Hz, 1H), 9.66 (s, 1H);

MS m/e 382 (MH^+).

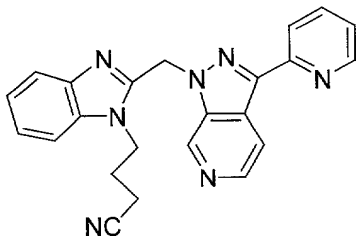


30

A mixture of compound **26** (40 mg, 0.1 mmol), 4-fluorophenylboronic acid (15 mg, 0.11 mmol), Cs_2CO_3 (49 mg, 0.15 mmol) and $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol) in DMF (1 ml) was heated to 100^{0}C for 4 h. Diluted with EtOAc (20 ml), washed with $NaHCO_3$, H_2O, and brine. Dried over $MgSO_4$ and concentrated. The residue was purified by prep-HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give compound **30** 16 mg (39%).

^{1}H NMR (CD_3OD) δ 2.24-2.30 (m, 2H), 2.64 (t, J=7.1 Hz, 2H), 4.72 (t, J=7.6 Hz, 2H), 6.45 (s, 2H), 7.30-7.34 (m, 2H), 7.39-7.42 (m, 1H), 7.46-7.49 (m, 1H), 7.64 (d, J=8.1 Hz, 1H), 7.76 (d, J=8.2 Hz, 1H), 8.07-8.10 (m, 1H), 8.51 (d, J=6.2 Hz, 1H), 8.55 (d, J=6.2 Hz, 1H), 9.72 (s, 1H);

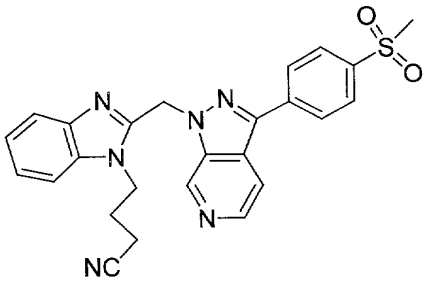
MS m/e 411 (MH^+).



31

Compound **31** was prepared using the same procedure as compound **21** starting with compound **26** and tributyl(2-pyridio)tin.

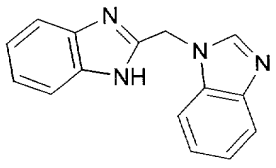
^{1}H NMR (CD_3OD) δ 2.30-2.36 (m, 2H), 2.71 (t, J=7.1 Hz, 2H), 4.77 (t, J=7.6 Hz, 2H), 6.57 (s, 2H), 7.44-7.49 (m, 2H), 7.50-7.54 (m, 1H), 7.67 (d, J=8.1 Hz, 1 H), 7.83 (d, J=8.2 Hz, 1H), 7.94-7.98 (m, 1H), 8.28 (d, J=8.0 Hz, 1H), 8.57-8.59 (m, 1H), 8.79 (d, J=4.3 Hz, 1H), 9.17-9.18 (m, 1H), 9.83 (s, 1H);
MS m/e 394 (MH^+).



32

Compound **32** was prepared using the same procedure as compound **21** starting with compound **26** and 4-methylsulfonylphenylboronic acid.

^{1}H NMR (CD_3OD) δ 2.27-2.33 (m, 2H), 2.67 (t, J=7.1 Hz, 2H), 4.75 (t, J=7.6 Hz, 2H), 6.53 (s, 2H), 7.42-7.45 (m, 1H), 7.49-7.52 (m, 1H), 7.66 (d, J=8.1 Hz, 1H), 7.79 (d, J=8.2 Hz, 1H), 8.10-8.13 (m, 2H), 8.29-8.32 (m, 2H), 8.57-8.60 (m, 2H), 9.77 (s, 1H);
MS m/e 471 (MH^+).



33

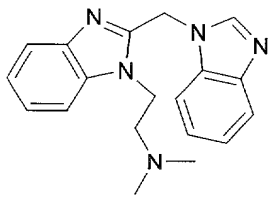
Compound **33** was prepared using the same procedure as compound **1c** starting with compound **1b** and benzimidazole:

^{1}H NMR ($CDCl_3$) δ 5.65 (s, 2H), 6.90-7.18 (m, 6H), 7.44 (s, 1H), 7.65 (bs, 2H);
IR (KBr, cm^{-1}) 1493, 1459, 1437, 1330, 1273, 745;

MS m/e 249 (MH^+);

Anal. Calcd for $C_{15}H_{12}N_4 \bullet 0.3\ H_2O$: C, 71.02; H, 5.01; N, 22.08

Found: C, 70.96; H, 4.86; N, 21.93.



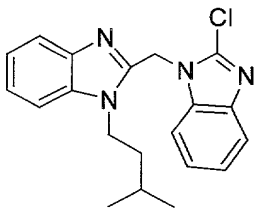
34

Compound **34** was prepared using the same procedure as compound **1** with compound **33** and 2-chloro-N,N-dimethylethylamine hydrochloride:

^1H NMR (CD_3OD) δ 3.14 (s, 6H), 3.94 (t, J = 7.6 Hz, 2H), 5.14 (t, J = 7.6 Hz, 2H), 6.79 (s, 2H), 7.52-7.80 (m, 6H), 7.80-8.12 (m, 2H);

IR (KBr, cm^{-1}) 3400, 2680, 1617, 1551, 1464, 1368, 756;

MS m/e 320 (MH^+).



35

To a solution of 2-chlorobenzimidazole (71 mg, 0.46 mmol) and NaH (60% suspension in mineral oil, 19 mg, 0.46 mmol) in DMF (2 mL) was added compound **4c** and the reaction was stirred at room temperature for 5 days. The solvent was evaporated *in vacuo* and the residue was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated. Purification by flash column chromatography (hexanes/EtOAc, 3:1) gave 43 mg (29% yield) of compound **35** as a white solid:

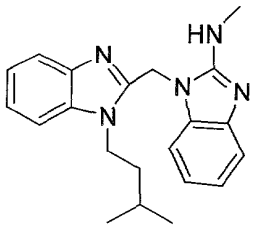
^{1}H NMR ($CDCl_3$) δ 0.83 (d, J = 6.7 Hz, 6 H), 1.06-1.14 (m, 2 H), 1.47-1.56 (m, 1 H), 4.05-4.11 (m, 2 H), 5.99 (s, 2 H), 7.21-7.30 (m, 2 H), 7.34-7.45 (m, 3 H), 7.54 (d, J = 7.1 Hz, 1 H), 7.69-7.72 (m, 1 H), 7.89-7.92 (m, 1 H);

IR (KBr, cm^{-1}) 3435, 2954, 1470, 1458, 1381, 744;

MS m/e 353 (MH^+);

Anal. Calcd for $C_{20}H_{21}ClN_4$: C, 68.08; H, 6.00; N, 15.88

Found: C, 67.82; H, 5.84; N, 15.58.



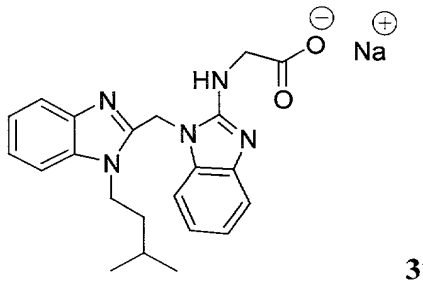
36

Compound **35** (150 mg, 0.43 mmol) and methylamine (165 mg, 2.13 mmol) were mixed in EtOH (2 mL) in a sealed tube. The reaction mixture was stirred at 125 °C for 18 hours. The EtOH was evaporated to give a light brown solid which was triturated with water to give 197 mg (100% yield) of compound **36**:

^{1}H NMR (DMSO-d_6) δ 0.90 (d, J = 6.6 Hz, 6 H), 1.32-1.40 (m, 2 H), 1.57-1.64 (m, 1 H), 2.94 (d, J = 4.4 Hz, 3 H), 4.21-4.27 (m, 2 H), 5.57 (s, 2 H), 6.84 (t, J = 7.2 Hz, 1 H), 6.96 (t, J = 7.2 Hz, 1 H), 7.10-7.26 (m, 4 H), 7.50 (d, J = 7.7 Hz, 1 H), 7.56 (d, J = 7.6 Hz, 1 H);

IR (KBr, cm^{-1}) 3375, 2955, 1668, 1622, 1577, 1462, 1331, 739;

MS m/e 348 (MH^+).

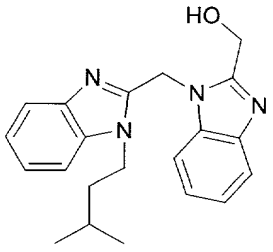


37

A mixture of glycine sodium salt hydrate (285 mg, 2.94 mmol) and compound **35** (207 mg, 0.59 mmol) in a mixture of water and EtOH (3 mL, 2:1) were stirred in a sealed tube at 120 °C for 9 days. The solvent was evaporated. The resulting solid was dissolved in water and the pH was adjusted to 7. The aqueous solution was extracted with EtOAc and the combined extracts were dried over $MgSO_4$ and evaporated. To the residue in MeOH was added 1 equivalent of 1N NaOH. The solvent was evaporated to give compound **37** as a brown solid:

^{1}H NMR (DMSO-d_6) δ 0.82 (d, J = 6.6 Hz, 6 H), 1.20-1.31 (m, 2 H), 1.48-1.54 (m, 1 H), 3.52 (d, J = 3.8 Hz, 2 H), 4.18-4.24 (m, 2 H), 5.57 (s, 2 H), 6.22 (t, J = 4.0 Hz, 1 H), 6.78-6.82 (m, 1 H), 6.89-6.94 (m, 1 H), 7.06-7.28 (m, 4 H), 7.47 (d, J = 7.5 Hz, 1 H), 7.58 (d, J = 8.4 Hz, 1 H);

MS m/e 392 (MH^+).



38

Compound **38** was prepared using the same procedure as compound **4** with 2-benzimidazolemethanol:

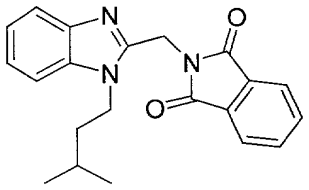
^{1}H NMR ($CDCl_3$) δ 0.87 (d, J = 6.5 Hz, 6 H), 1.32-1.40 (m, 2 H), 1.48-1.55 (m, 1 H), 4.14-4.19 (m, 2 H), 4.87 (s, 2 H), 5.72 (s, 2 H), 7.28-7.40 (m, 6 H), 7.72-7.79 (m, 2 H);

IR (KBr, cm^{-1}) 2948, 1473, 1458, 1438, 1400, 1035, 740;

MS m/e 349 (MH^+);

Anal. Calcd for $C_{21}H_{24}N_4O \bullet 0.25\ H_2O$: C, 71.46; H, 7.00; N, 15.87

Found: C, 71.23; H, 6.99; N, 15.90.



39

Compound **39** was prepared using the same procedure as compound **4** with phthalimide in 26% yield:

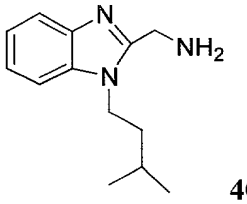
^{1}H NMR ($CDCl_3$) δ 1.00 (d, J = 6.2 Hz, 6H), 1.67-1.81 (m, 3H), 4.30 (t, J = 7.9 Hz, 2H), 5.11 (s, 1H), 7.17-7.32 (m, 4H), 7.68-7.76 (m, 2H), 7.85-7.91 (m, 2H);

IR (KBr, cm^{-1}) 2953, 1774, 1718, 1469, 1424, 1394, 1323, 1115, 950, 749, 723;

MS m/e 348 (MH^+);

Anal. Calcd for $C_{21}H_{21}N_3O_2 \bullet 0.5\ H_2O$: C, 70.77; H, 6.22; N, 11.79

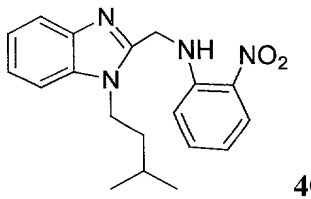
Found: C, 70.76; H, 6.39; N, 11.62.



40a

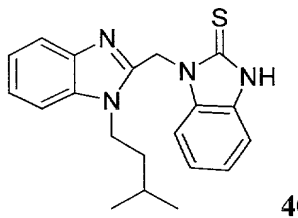
Compound **39** (2.0 g, 6.00 mmol) was stirred at reflux with excess hydrazine hydrate (617 mg, 17.61 mmol) in EtOH for 2 hours. The reaction mixture was diluted with EtOH and the precipitate was filtered and washed with

EtOH. The filtrate was concentrated, diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated to give 967 mg (74% yield) of compound **40a** as a brown oil which was used without further purification.



40b

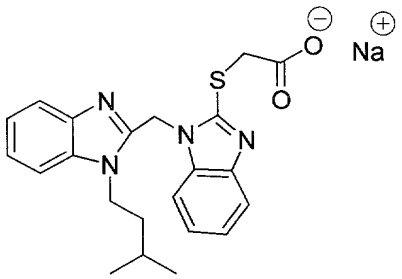
A mixture of amine **40a** (960 mg, 4.42 mmol), 1-fluoro-2-nitrobenzene (811 mg, 5.75 mmol), and K_2CO_3 (732 mg, 5.03 mmol) in CH_3CN was stirred at reflux for 18 hours. The reaction mixture was filtered and washed with EtOAc. The filtrate was concentrated, subjected to flash column chromatography (gradient, hexanes/EtOAc, 3:1 to 2:1), and recrystallized from Et_2O/hexanes to give 486 mg (32% yield) of compound **40b** as an orange solid.



40

Compound **40b** (1.0 g, 2.96 mmol) was reduced under H_2 in a Parr apparatus in the presence of 10% palladium on carbon (150 mg) in a mixture of EtOAc and MeOH (22 mL, 10:1) at 60 psi for 45 minutes. The catalyst was removed by filtration through a pad of celite and the filtrate was concentrated. This diamine was then treated with 1,1'-thiocarbonyldiimidazole (686 mg, 3.85 mmol) in THF and stirred at reflux for 5 hours. The solvent was concentrated and the residue was subjected to flash column chromatography (hexanes/EtOAc, 2:1) to give 835 mg (81% yield) of compound **40**:

^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 6.6 Hz, 6H), 1.34-1.42 (m, 2H), 1.64-1.73 (m, 2H), 4.39 (bt, J = 8.0 Hz, 2H), 5.83 (s, 2H), 7.10-7.27 (m, 5H), 7.37 (d, J = 7.4 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 13.03 (s, 1H);
MS m/e 351 (MH^+).

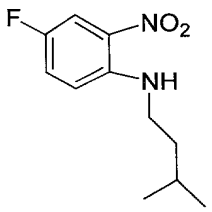


41

A mixture of compound **40** (150 mg, 0.43 mmol), bromoacetic acid (65 mg, 0.47 mmol) and K_2CO_3 (65 mg, 0.47 mmol) in CH_3CN (2 mL) were stirred at room temperature for 3 days. Additional bromoacetic acid (60 mg, 0.43 mmol) in CH_3CN (2 mL) was added and the reaction mixture was refluxed for 4 hours. The solvent was evaporated. The residue was diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The aqueous layer was then neutralized to pH 7 and extracted with EtOAc. The extracts were dried over $MgSO_4$ and evaporated to give 77 mg (44% yield) of compound **41** as a pale brown solid.

A mixture of acid **41** (125 mg, 0.31 mmol) and 1N NaOH (0.31 mL, 0.31 mmol) in MeOH (3 mL) was stirred at room temperature and was evaporated to give a light green product. This material was dissolved in water, treated with active carbon and filtered. The filtrate was concentrated to give 107 mg (80% yield) of the sodium salt of compound **41**:

^{1}H NMR (DMSO-d_6) δ 0.85 (d, J = 6.6 Hz, 6 H), 1.23-1.33 (m, 2 H), 1.51-1.60 (m, 2 H), 3.82 (s, 2 H), 4.22-4.28 (m, 2 H), 5.72 (s, 2 H), 7.03-7.26 (m, 4 H), 7.36 (d, J = 7.0 Hz, 1 H), 7.48-7.57 (m, 3 H);
MS m/e 409 (MH^+).

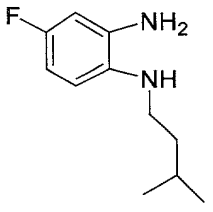


42a

To a solution of 2,5-difluoronitrobenzene (45 g, 282.86 mmol) in CH_3CN (500 mL) was added potassium carbonate (78 g, 565.72 mmol) and isoamylamine (25 g, 282.86 mmol). The reaction mixture was stirred at room temperature for 18 hours with the aid of a mechanical stirrer. The potassium carbonate was filtered and the filtrate was evaporated to give an orange oil. The oil was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and evaporated. Purification by flash column chromatography (hexanes/EtOAc, 20:1) gave 53 g (83% yield) of compound **42a**:

^1H NMR ($CDCl_3$) δ 0.98 (d, J = 6.5 Hz, 6H), 1.61-1.65 (m, 2H), 1.74-1.78 (m, 1H), 3.30 (t, J = 7.3 Hz, 2H), 6.83 (dd, J = 4.6, 9.5 Hz, 1H), 7.23-7.27 (m, 1H), 7.85 (dd, J = 3.1, 9.2 Hz, 1H);

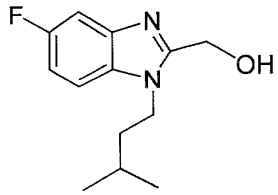
MS m/e 226 (MH^+).



42b

To a solution of compound **42a** (53 g, 235.14 mmol) and concentrated HCl (15 mL) in MeOH (200 mL) was added 10% palladium on carbon (5 g) and the mixture was reduced under H_2 at 55 psi for 1.5 hours. The catalyst was removed by filtration through a pad of celite and the filtrate was concentrated to give 47 g (87% yield) of diamine **42b** as the HCl salt:

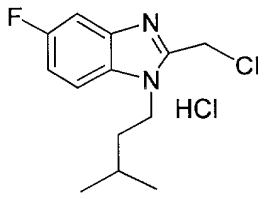
^{1}H NMR ($CDCl_3$) δ 0.97 (d, J = 6.2 Hz, 6 H), 1.65-1.77 (m, 3 H), 3.36 (t, J = 8.0 Hz, 2 H), 6.50-6.57 (m, 1 H), 6.71 (dd, J = 2.7, 10.5 Hz, 1 H), 7.28 (dd, J = 5.5, 8.8 Hz, 1 H);
MS m/e 197 (MH^+).



42c

A mixture of diamine **42b** (47 g, 200.66 mmol) and glycolic acid (16 g, 210.70 mmol) in 4N HCl (500 mL) were stirred at reflux for 18 hours. The reaction mixture was cooled to 0 °C and was adjusted to pH 8 by adding concentrated ammonium hydroxide. The product was extracted with EtOAc, dried over $MgSO_4$, and evaporated. The crude product was recrystallized with EtOAc/hexanes to give 27 g (37% yield) of compound **42c** as brown crystals:

^{1}H NMR ($CDCl_3$) δ 1.02 (d, J = 6.0 Hz, 6 H), 1.68-1.75 (m, 3 H), 3.19 (bs, 1 H), 4.22 (t, J = 7.7 Hz, 2 H), 4.93 (s, 2 H), 7.06 (dt, J = 2.2, 9.1 Hz, 1 H), 7.26-7.28 (m, 1 H), 7.37 (dd, J = 2.1, 8.9 Hz, 1 H);
MS m/e 237 (MH^+).

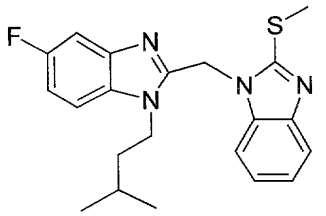


42d

To a solution of alcohol **42c** (27 g, 112.99 mmol) in CH_2Cl_2 (100 mL) was slowly added thionyl chloride (27g, 225.99 mmol) and the reaction mixture was stirred at 65 °C for 2.5 hours. The solvent and excess thionyl chloride were evaporated to give a grey solid. The solid was suspended in Et_2O and evaporated

several times to ensure removal of the solvent and reagent. The solid was then dissolved in a minimal amount of CH_2Cl_2 and precipitated by addition of hexanes. The solid was collected by filtration and triturated with Et_2O to give 32 g (96% yield) of compound **42d** as a grey solid:

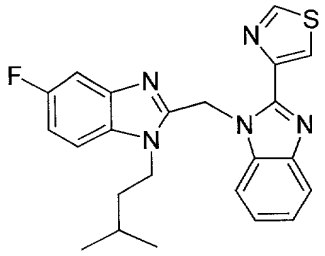
^{1}H NMR ($CDCl_3$) δ 1.08 (d, J = 6.4 Hz, 6H), 1.79-1.90 (m, 3H), 4.44 (bt, J = 8.2 Hz, 2H), 5.32 (s, 2H), 7.36 (dt, J = 2.2, 8.9, 1H), 7.54-7.59 (m, 2H);
MS m/e 255 (MH^+).



42

Compound **42** was prepared using the same procedure as compound **4** with compound **42d** and 2-(methylmercapto)benzimidazole in 95% yield:

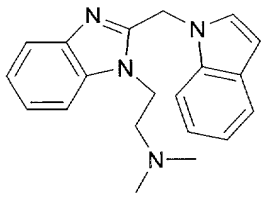
^{1}H NMR (CD_3OD) δ 0.99 (d, J = 6.5 Hz, 6 H), 1.61-1.66 (m, 2 H), 1.66-1.71 (m, 1 H), 2.91 (s, 3 H), 4.40-4.43 (m, 2 H), 6.05 (s, 2 H), 7.21 (td, J = 2.4, 9.2 Hz, 1 H), 7.27 (dd, J = 2.4, 8.9 Hz, 1 H), 7.43-7.51 (m, 2 H), 7.63-7.65 (m, 2 H), 7.76 (d, J = 7.8 Hz, 1 H);
MS m/e 384 (MH^+).



43

Compound **43** was prepared using the same procedure as compound **4** with compound **42d** and thiabenazole in 67% yield:

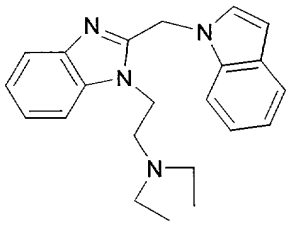
^{1}H NMR (CD_3OD) δ 1.02 (d, J = 6.2 Hz, 6 H), 1.72-1.74 (m, 3 H), 4.45-4.48 (m, 2 H), 6.56 (s, 2 H), 7.17-7.21 (m, 2 H), 7.46-7.53 (m, 2 H), 7.62-7.64 (m, 1 H), 7.72 (d, J = 8.1 Hz, 1 H), 7.84 (d, J = 7.8 Hz, 1 H), 8.61 (s, 1 H), 9.09 (s, 1 H); MS m/e 420 (MH^+).



44

Compound **44** was prepared using the same procedure sequence as compound **1** starting with indole:

^{1}H NMR ($CDCl_3$) δ 2.01 (bs, 8 H), 4.02 (t, J = 7.3 Hz, 2 H), 5.64 (s, 2 H), 6.55 (dd, J = 0.8, 3.2 Hz, 1 H), 7.08-7.29 (m, 6 H), 7.48 (d, J = 8.6 Hz, 1 H), 7.62 (d, J = 7.5 Hz, 1 H), 7.80-7.84 (m, 1 H);
IR (KBr, cm^{-1}) 2943, 2824, 1613, 1463, 1420, 1323, 741;
MS m/e 319 (MH^+).



45

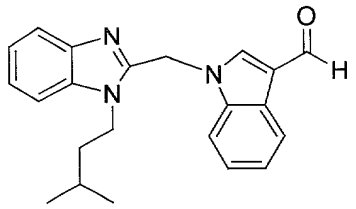
Compound **45** was prepared using the same procedure sequence as compound **1** starting with indole and 2-chloro-N,N-diethylethylamine hydrochloride:

^{1}H NMR (CD_3OD) δ 1.31 (t, J = 7.3 Hz, 6 H), 3.10 (t, J = 8.1 Hz, 2H), 3.60-3.75 (m, 4 H), 4.94 (s, 2 H), 4.99-5.04 (m, 2 H), 6.75 (d, J = 8.0 Hz, 1 H), 6.81 (t, J =

7.5 Hz, 1 H), 7.10 (t, J = 7.4 Hz, 1 H), 7.19 (d, J = 7.2 Hz, 1 H), 7.62-7.72 (m, 4 H), 7.82 (d, J = 7.2 Hz, 8.06 (d, J = 7.4 Hz, 1 H);

IR (KBr, cm^{-1}) 3396, 2925, 1728, 1606, 1523, 1464, 1253, 1136, 753;

MS m/e 349 (MH^+).



46

To a suspension of indole-3-carboxaldehyde (129 mg, 0.89 mmol) in CH_3CN was added NaH (60% suspension in mineral oil, 39 mg, 0.98 mmol). After stirring for 15 minutes, the neutral form of compound **4c** (232 mg, 0.98 mmol) was added. The reaction mixture was stirred at room temperature for 2.5 hours and then heated to 70 °C for 1.5 hours. After evaporation of the solvent, the resulting residue was diluted with aqueous saturated $NaHCO_3$ and extracted with EtOAc. The organic extracts were dried over $MgSO_4$ and evaporated. Column chromatography (gradient, hexanes/EtOAc, 1:1 to EtOAc/hexanes, 2:1) gave 199 mg (65% yield) of compound **46**:

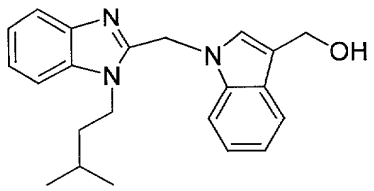
^1H NMR ($CDCl_3$) δ 0.68 (d, J = 6.6 Hz, 6 H), 1.05-1.13 (m, 2 H), 1.23-1.36 (m, 1 H), 3.87-3.93 (m, 2 H), 5.60 (s, 2 H), 7.22-7.33 (m, 4 H), 7.47-7.54 (m, 1 H), 7.70 (s, 1 H), 7.75-7.80 (m, 1 H), 8.23-8.27 (m, 1 H), 9.90 (s, 1 H);

IR (KBr, cm^{-1}) 3432, 2961, 1662, 1651, 1526, 1463, 1386, 1189, 1171, 1038, 778, 739;

MS m/e 346 (MH^+);

Anal. Calcd for $C_{22}H_{23}N_3O \bullet 0.25\ H_2O$: C, 75.51; H, 6.77; N, 12.01

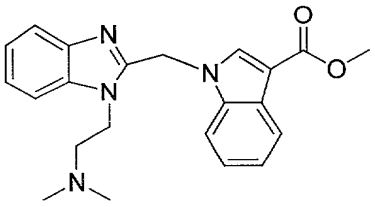
Found: C, 75.60; H, 6.59; N, 11.83.



47

Sodium borohydride (10 mg, 0.26 mmol) was added to a solution of aldehyde **46** (70 mg, 0.20 mmol) in MeOH (5 mL) at 0 °C. The reaction was monitored by thin layer chromatography and when complete, the solvent was evaporated. The resulting residue was subjected to flash column chromatography (straight EtOAc) to give 50 mg (70% yield) of compound **47** as a white solid:

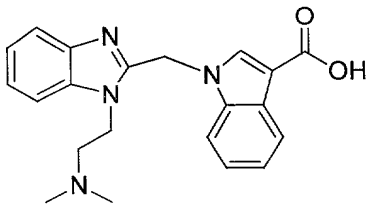
^{1}H NMR ($CDCl_3$) δ 0.71 (d, J = 6.6 Hz, 6 H), 1.04-1.12 (m, 2 H), 1.22-1.33 (m, 1 H), 3.87-3.92 (m, 2 H), 4.82 (s, 2 H), 5.56 (s, 2 H), 7.12 (s, 1 H), 7.14-7.31 (m, 5 H), 7.47 (d, J = 8.2 Hz, 1 H), 7.71-7.74 (m, 1 H), 7.80-7.83 (m, 1 H);
IR (KBr, cm^{-1}) 3247, 2950, 2867, 1612, 1465, 1309, 1038, 743;
MS m/e 348 (MH^+);
Anal. Calcd for $C_{22}H_{25}N_3O \bullet 0.25\ H_2O$: C, 75.08; H, 7.30; N, 11.94
Found: C, 74.86; H, 7.17; N, 11.82.



48

Compound **48** was prepared using the same procedure sequence as compound **1** starting with methyl indole-4-carboxylate:

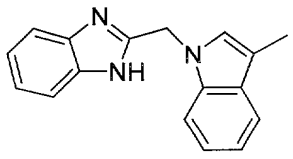
^{1}H NMR ($CDCl_3$) δ 2.00 (s, 6 H), 2.13 (t, J = 6.9 Hz, 2 H), 3.81 (s, 3 H), 4.00 (t, J = 6.9 Hz, 2 H), 5.63 (s, 2 H), 7.21-7.26 (m, 5 H), 7.50 (dd, J = 2.4, 5.9 Hz, 1 H), 7.76 (dd, J = 4.5, 7.5 Hz, 1 H), 7.79 (s, 1 H), 8.13 (dd, J = 0.3, 6.2 Hz, 1 H);
MS m/e 377 (MH^+).



49

A mixture of methyl ester **48** (45 mg, 0.12 mmol) and sodium hydroxide (480 mg, 12.00 mmol) in MeOH (15 mL) was stirred at room temperature for 2 hours and then heated at reflux for 4 days. The solution was neutralized with 1N HCl and the solvent was evaporated. The product was dissolved in cold MeOH and decanted from the solids. The solvent was evaporated to give compound **49**:

^{1}H NMR (CD_3OD) δ 2.93 (s, 6 H), 3.30-3.34 (m, 2 H), 4.87-4.92 (m, 2 H), 6.16 (s, 2 H), 7.27-7.30 (m, 2 H), 7.42-7.54 (m, 2 H), 4.63 (dd, J = 3.0, 6.8 Hz, 1 H), 7.67 (d, J = 7.5 Hz, 1 H), 7.89 (d, J = 6.4 Hz, 1 H), 8.17-8.20 (m, 1 H), 8.23 (s, 1 H);
MS m/e 361 (MH^-).

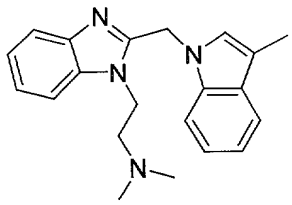


50

To a solution of 3-methylindole (390 mg, 2.97 mmol) in CH_3CN was added NaH (60% suspension in mineral oil, 72 mg, 2.97 mmol) and the mixture was stirred at room temperature for 1 hour. Compound **1b** was added and the mixture was stirred at room temperature for 17 hours. The solvent was evaporated and the residue was diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$, and concentrated. Purification by flash column chromatography (hexanes/EtOAc, 4:1) gave the mesyl protected intermediate.

The mesyl protecting group was removed by stirring the mesyl protected intermediate (25 mg, 0.07 mmol) with excess hydrazine hydrate (2 mL) in MeOH

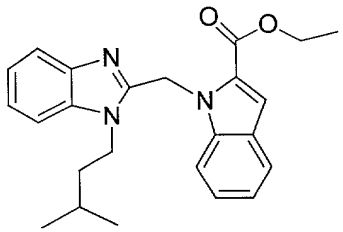
(5 mL) at reflux. The solvent was evaporated and the residue was diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$, and concentrated. Intermediate **50** was used without further purification.



51

To a mixture of **50** (10 mg, 0.04 mmol) and NaH (60% suspension in mineral oil, 4 mg, 0.1 mmol) in THF (1 mL) was added 2-chloro-N,N-dimethylethylamine hydrochloride (6 mg, 0.04 mmol) and the mixture was stirred at reflux for 24 hours. The solvent was evaporated and the residue was diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$, and concentrated. Purification by flash column chromatography (straight EtOAc) gave 6 mg (46% yield) of compound **51**:

^{1}H NMR ($CDCl_3$) δ 2.00 (s over t, J = 7.5 Hz, 8 H), 2.27 (s, 3 H), 4.01-4.06 (t, J = 7.5 Hz, 2 H), 5.57 (s, 2 H), 6.89 (s, 1 H), 6.89-7.32 (m, 5 H), 7.44 (d, J = 8.9 Hz, 1 H), 7.56 (d, J = 8.7 Hz, 1 H), 7.80-7.83 (m, 1 H);
MS m/e 333 (MH^+).



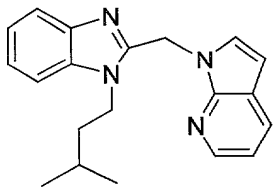
52

Compound **52** was prepared using the same procedure as compound **4** with compound **4c** and ethyl indole-2-carboxylate:

^{1}H NMR ($CDCl_3$) δ 0.80 (d, J = 6.6 Hz, 6 H), 1.02-1.09 (m, 3 H), 1.41 (t, J = 7.1 Hz, 3 H), 4.02-4.07 (m, 2 H), 4.39 (q, J = 7.1 Hz, 2 H), 6.30 (s, 2 H), 7.11 (t, J = 7.1 Hz, 1 H), 7.19-7.25 (m, 4 H), 7.44 (s, 1 H), 7.60-7.66 (m, 2 H), 7.76-7.80 (m, 1 H);

IR (KBr, cm^{-1}) 2956, 2871, 1699, 1519, 1458, 1325, 1257, 1194, 1139, 1096, 743;

MS m/e 390 (MH^+).

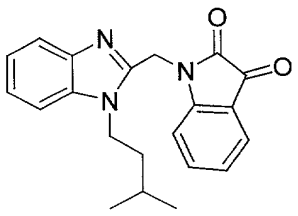


53

Compound **53** was prepared using the same procedure as compound **4** with compound **4c** and 7-azaindole:

^{1}H NMR ($CDCl_3$) δ 0.57 (d, J = 6.6 Hz, 6 H), 0.86-0.97 (m, 2 H), 1.04-1.13 (m, 1 H), 3.99-4.05 (m, 2 H), 5.77 (s, 2 H), 6.41 (d, J = 3.6 Hz, 1 H), 7.05 (dd, J = 4.7, 7.8 Hz, 1 H), 7.19-7.25 (m, 4 H), 7.33-7.76 (m, 1 H), 7.86 (dd, J = 1.6, 7.8 Hz, 1 H), 8.31 (dd, J = 1.4, 4.7 Hz, 1 H);

MS m/e 319 (MH^+).

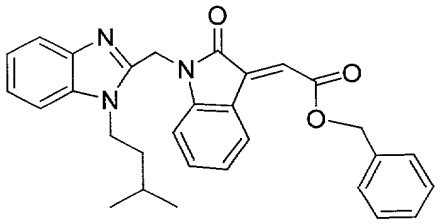


54

To a solution of isatin (7.35 g, 50.0 mmol) in DMF (250 ml) at 0 °C was added NaH (5.0 g, 60% dispersion, 125 mmol). The resulting mixture was stirred at 0 °C for 30 minutes and then chloride **4c** (13.0 g, 55.0 mmol) was added. After stirring for additional 2 hours, the mixture was diluted with EtOAc (250 ml),

washed with saturated NH_4Cl and water (250 ml x 2), brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (gradient, hexane:EtOAc = 3:1 to 1:2) to give 11.6 g (67% yield) of compound **54** as an orange solid:

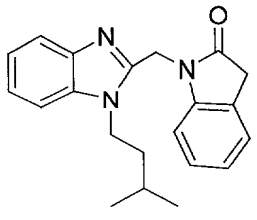
^1H NMR (CD_3OD) δ 0.96 (d, J = 6.6 Hz, 6 H), 1.54-1.57 (m, 2 H), 1.65-1.75 (m, 1 H), 4.21-4.26 (m, 2 H), 5.24 (s, 2 H), 7.10-7.11 (m, 1 H), 7.26-7.32 (m, 3 H), 7.54-7.59 (m, 3 H), 7.76-7.78 (m, 1 H);
MS m/e 348 (MH^+).



55

The isatin compound **54** (416 mg, 1.20 mmol) and benzyl (triphenylphosphoranylidene) acetate (540 mg, 1.32 mmol) were stirred in CH_2Cl_2 for 1 hour. The solvent was evaporated and column chromatography (20% EtOAc in hexanes) gave 350 mg (60% yield) of compound **55**:

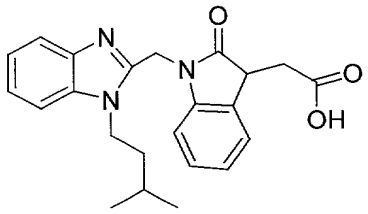
^1H NMR ($CDCl_3$) δ 0.91 (d, J = 6.6 Hz, 6 H), 1.39-1.47 (m, 2 H), 1.59-1.73 (m, 2 H), 4.19-4.24 (m, 2 H), 5.29 (s, 2 H), 5.31 (s, 2 H), 6.99-7.04 (m, 2 H), 7.25-7.32 (m, 4 H), 7.35-7.43 (m, 6 H), 7.27-7.80 (m, 1 H), 8.50 (d, J = 7.5 Hz, 1 H);
MS m/e 480 (MH^+).



56

Compound **55** (100 mg, 0.21 mmol) was treated with hydrazine (13 mg, 0.42 mmol) in ethanol (5 mL) and heated at 60 °C for 16 hours. Solvent was evaporated and column chromatography (10% EtOAc in hexanes) gave compound **56** as a white solid:

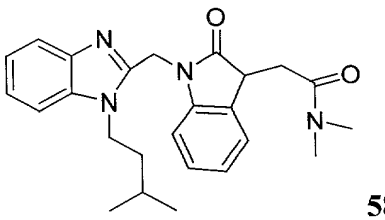
^{1}H NMR ($CDCl_3$) δ 0.97 (d, J = 6.5 Hz, 6 H), 1.45-1.52 (m, 2 H), 1.65-1.76 (m, 1 H), 3.59 (s, 2 H), 4.23-4.29 (m, 2 H), 5.27 (s, 2 H), 7.01 (t, J = 7.0 Hz, 1 H), 7.18-7.33 (m, 5 H), 7.41 (d, J = 7.9 Hz, 1 H), 7.76-7.80 (m, 1 H);
MS m/e 334 (MH^+).



57

To a solution of compound **55** (100 mg, 0.21 mmol) in EtOAc (7 mL) was added 10% palladium on carbon (25 mg). The solution was agitated under H_2 at 50 psi for 3 hours. The reaction mixture was diluted with MeOH and the catalyst was filtered through a pad of celite. The filtrate was concentrated and the residue was washed with EtOAc to give 60 mg (73 % yield) of compound **57** as a light green solid:

^{1}H NMR ($CDCl_3$) δ 0.94 (d, J = 6.5 Hz, 6 H), 1.46-1.70 (m, 3 H), 2.81 (dd, J = 6.8, 17.0 Hz, 1 H), 2.97 (dd, J = 4.8, 17.0 Hz, 1 H), 3.81 (t, J = 5.6 Hz, 1 H), 4.25-4.30 (m, 2 H), 5.09 (d, J = 16.0 Hz, 1 H), 5.24 (d, J = 16.0 Hz, 1 H), 6.95-7.01 (m, 1 H), 7.06-7.25 (m, 4 H), 7.29 (d, J = 7.2 Hz, 1 H), 7.49 (d, J = 7.7 Hz, 1 H), 7.59 (d, J = 7.6 Hz, 1 H), 12.41 (s, 1 H);
MS m/e 392 (MH^+).

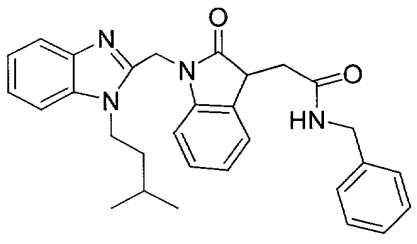


58

Acid **57** (120 mg, 0.31 mmol), dimethyl amine hydrochloride (25 mg, 0.31 mmol), HOBT (46 mg, 0.34 mmol), N-methylmorpholine (85 mg, 0.84 mmol), and EDAC (65 mg, 0.34 mmol) were stirred in anhydrous DMF (1 mL) for 16 hours at room temperature. The reaction mixture was diluted with EtOAc and water. An insoluble white solid was filtered and triturated in EtOAc to give compound **58**:

^{1}H NMR ($CDCl_3$) δ 0.96 (d, J = 6.4 Hz, 3 H), 0.98 (d, J = 6.4 Hz, 3 H), 1.41-1.76 (m, 3 H), 2.75 (dd, J = 9.0, 16.5 Hz, 1 H), 2.98 (s, 3 H), 2.99 (s, 3 H), 3.16 (dd, J = 3.1, 16.6 Hz, 1 H), 4.01 (dd, J = 3.0, 9.0 Hz, 1 H), 4.27 (t, J = 8.2 Hz, 2 H), 5.08 (d, J = 15.4 Hz, 1 H), 5.42 (d, J = 15.4 Hz, 1 H), 6.95-7.00 (m, 1 H), 7.16-7.32 (m, 5 H), 7.41 (d, J = 7.8 Hz, 1 H), 7.74-7.78 (m, 1 H);

MS m/e 419 (MH^+).

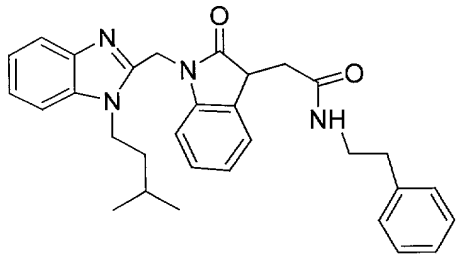


59

Compound **59** was prepared using the same procedure as compound **58** with benzyl amine:

^{1}H NMR ($CDCl_3$) δ 0.96 (d, J = 6.4 Hz, 3 H), 0.98 (d, J = 6.4 Hz, 3 H), 1.42-1.75 (m, 3 H), 2.70 (dd, J = 7.2, 15.4 Hz, 1 H), 3.02 (dd, J = 5.7, 15.4 Hz, 1 H), 3.95 (t, J = 6.3 Hz, 1 H), 4.28 (t, J = 8.1 Hz, 2 H), 4.45 (t, J = 5.0 Hz, 2 H), 5.11 (d, J =

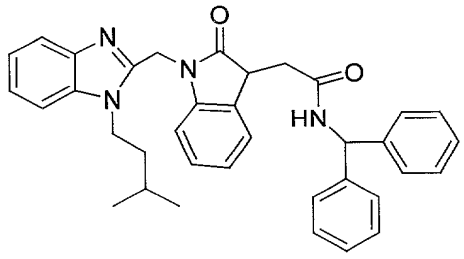
15.4 Hz, 1 H), 5.42 (d, J = 15.4 Hz, 1 H), 6.49-6.61 (m, 1 H), 6.94-7.02 (m, 1 H), 7.21-7.33 (m, 10 H), 7.44 (d, J = 7.9 Hz, 1 H), 7.74-7.66 (m, 1 H);
MS m/e 481 (MH^+).



60

Compound **60** was prepared using the same procedure as compound **58** with phenethylamine:

^1H NMR ($CDCl_3$) δ 0.97 (d, J = 6.5 Hz, 6 H), 1.40-1.93 (m, 3 H), 2.51 (q, J = 7.9 Hz, 1 H), 2.78-2.96 (m, 3 H), 3.50-3.62 (m, 2 H), 3.91-3.96 (m, 1 H), 4.24 (t, J = 8.1 Hz, 2 H), 5.04 (d, J = 15.4 Hz, 1 H), 5.35 (d, J = 15.4 Hz, 1 H), 6.07 (t, J = 5.6 Hz, 1 H), 7.00 (t, J = 7.5 Hz, 1 H), 7.15-7.32 (m, 10 H), 7.40 (d, J = 7.6 Hz, 1 H), 7.72-7.77 (m, 1 H);
MS m/e 495 (MH^+).

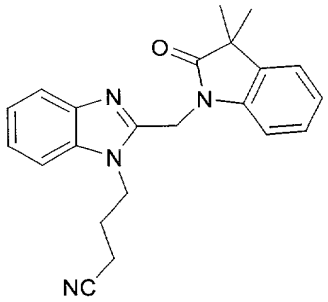


61

Compound **61** was prepared using the same procedure as compound **58** with aminodiphenylmethane:

^1H NMR ($CDCl_3$) δ 0.94 (d, J = 6.4 Hz, 3 H), 0.96 (d, J = 6.4 Hz, 3 H), 1.39-1.71 (m, 3 H), 2.70 (dd, J = 7.1, 15.4 Hz, 1 H), 3.03 (dd, J = 6.2, 15.4 Hz, 1 H), 3.97 (t,

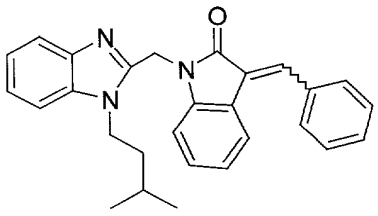
J = 6.6 Hz, 1 H), 4.22 (t, J = 8.2 Hz, 1 H), 5.03 (d, J = 15.4 Hz, 1 H), 5.34 (d, J = 15.4 Hz, 1 H), 6.27 (d, J = 8.0 Hz, 1 H), 6.90-7.05 (m, 2 H), 7.15-7.36 (m, 14 H), 7.41 (d, J = 7.8 Hz, 1 H), 7.72-7.77 (m, 1 H);
MS m/e 557 (MH^+).



62

To a solution of 1,3-dihydro-3,3-dimethyl-2H-indol-2-one (100 mg, 0.62 mmol) in THF (20 mL) was added BTPP (0.61 g, 1.98 mmol). The solution was stirred for 15 minutes and then the compound **25b** (168 mg, 0.61 mmol) was added and the mixture was stirred for 3 days at room temperature. The solvent was removed and the residue was washed with water. (20 mL, 10x) to give 110 mg (50% yield) of compound **62** as a clear glass:

^1H NMR (DMSO-d_6) δ 1.41 (s, 6 H), 2.05-2.08 (m, 2 H), 2.48 (t, J = 4.3 Hz, 2 H), 4.25-4.56 (m, 2 H), 5.25 (s, 2 H), 7.07 (t, J = 4.47 Hz, 1 H), 7.18-7.39 (m, 4 H), 7.55 (d, J = 4.7 Hz, 2 H), 7.81 (d, J = 4.1 Hz, 1 H);
MS m/e 357 (MH^+).

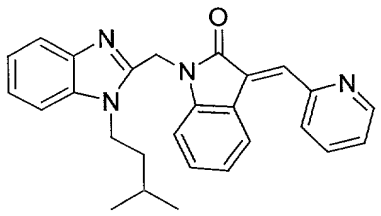


63

To a solution of benzyltriphenylphosphonium chloride (129 mg, 0.33 mmol) in CH_2Cl_2 was added NaH (16 mg, 0.39 mmol) and the mixture was

stirred for 30 minutes. This solution was added dropwise to a solution of the isatin compound **54** in CH_2Cl_2. The reaction mixture was allowed to stir for 1 hour, was diluted with EtOAc, and washed with H_2O. The organic layer was dried over $MgSO_4$ and evaporated. Column chromatography (20% EtOAc in hexanes) gave compound **63** as a 2:1 mixture of regioisomers:

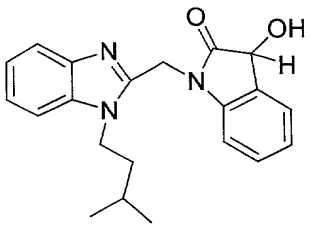
^{1}H NMR ($CDCl_3$) δ 0.82, 0.93 (d, J = 6.6 Hz, 6 H), 1.32-1.46 (m, 2 H), 1.53-1.77 (m, 1 H), 4.20-4.31 (m, 2 H), 6.85, 7.03 (td, J = 1.0, 7.7 Hz, 1 H), 7.15-7.21 (m, 1 H), 7.25-7.39 (m, 4 H), 7.43-7.50 (m, 3 H), 7.63 (bs, 1 H), 7.60,7.93 (s,1 H), 7.62-7.66, 8.29-8.33 (m, 1 H);
MS m/e 422 (MH^+).



64

Compound **64** was prepared using the same procedure as compound **63** with triphenyl(2-pyridylmethyl)-phosphonium chloride hydrochloride:

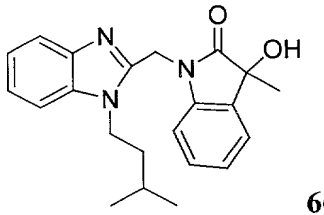
^{1}H NMR ($CDCl_3$) δ 0.89 (d, J = 6.6 Hz, 6 H), 1.39-1.47 (m, 2 H), 1.64-1.73 (m, 1 H), 4.25-4.31 (m, 2 H), 5.38 (s, 2 H), 7.03 (t, J = 7.2 Hz, 1 H), 7.22-7.41 (m, 6 H), 7.63 (d, J = 7.8 Hz, 1 H), 7.78-7.83 (m, 3 H), 8.86 (d, J = 3.7 Hz, 1 H), 9.02 (d, J = 7.5 Hz, 1 H);
MS m/e 423 (MH^+).



65

To a solution of compound **54** (102 mg, 0.29 mmol) in MeOH (5 mL) was added 10% palladium on carbon (20 mg) and the mixture was aggitated on a Parr apparatus under H_2 at 50 psi for 18 hours. The catalyst was filtered through a pad of celite and the filtrate was evaporated. The residue was triturated in a mixture of Et_2O and hexanes and then filtered to give 70 mg (69% yield) of compound **65**:

^{1}H NMR ($CDCl_3$) δ 0.98 (d, J = 6.6 Hz, 6 H), 1.48-1.76 (m, 3 H), 3.28 (bs, 1 H), 4.19-4.25 (m, 2 H), 5.10 (s, 1 H), 5.13 (d, J = 15.5 Hz, 1 H), 5.22 (d, J = 15.5 Hz, 1 H), 7.07 (t, J = 7.0 Hz, 1 H), 7.23-7.30 (m, 4 H), 7.35 (d, J = 7.7 Hz, 1 H), 7.42 (d, J = 7.4 Hz, 1 H), 7.73-7.77 (m, 1 H);
IR (KBr, cm^{-1}) 3423, 2956, 1720, 1615, 1468, 1369, 1172, 743;
MS m/e 378 (MH^+);
Anal. Calcd for $C_{21}H_{24}N_3O_2$: C, 71.98; H, 6.90; N, 11.99
Found: C, 71.67; H, 6.57; N, 11.66.

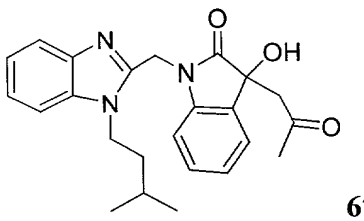


66

To a round bottom flask charged with methyl lithium in ether (1.4 M, 1.18 mL, 1.65 mmol) was added $ZnCl_2$ in ether (1.0 M, 1.27 mL, 1.27 mmol) at –78°C. The mixture was allowed to stir for 1 hour. Compound **54** (442 mg, 1.27 mmol) was added and the mixture was stirred at –78 °C for 1 hour. The temperature was raised to 21 °C. Column chromatography (gradient, 15 – 20 % EtOAc in hexanes) gave compound **66** as a yellow solid:

^{1}H NMR ($CDCl_3$) δ 1.05 (d, J = 6.2 Hz, 6 H), 1.65 (s, 3 H), 1.69-1.82 (m, 3 H), 4.19-4.30 (m, 2 H), 4.88 (d, J = 16.4 Hz, 1H), 5.44 (d, J = 16.4 Hz, 1 H), 6.90 (d, J = 7.8 Hz, 1 H), 7.09 (t, J = 7.5 1 H), 7.18-7.37 (m, 4 H), 7.46 (dd, J = 1.0, 7.3 Hz, 1 H), 7.62 (d, J = 7.1 Hz, 1 H).

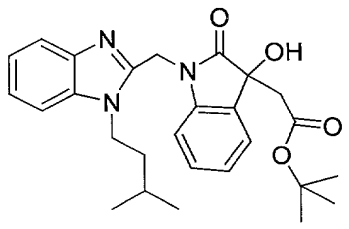
MS m/e 364 (MH^+).



67

A mixture of compound **54** (200 mg, 0.58 mmol) and K_2CO_3 (1.5 g, 10.85 mmol) in acetone were stirred at reflux for 30 minutes. The solvent was evaporated and the residue was taken up in EtOAc. Column chromatography (gradient, 30-50% EtOAc in hexanes) gave compound **67** as a yellow solid:

^1H NMR ($CDCl_3$) δ 0.98 (t, J = 6.2 Hz, 6 H), 1.53-1.77 (m, 3 H), 2.15 (s, 3 H), 3.06 (d, J = 17.2 Hz, 1 H), 3.25 (d, J = 17.2 Hz, 1 H), 4.19 (t, J = 8.1 Hz, 2 H), 4.98 (d, J = 15.7 Hz, 1 H), 5.26 (d, J = 15.7 Hz, 1 H), 7.00 (dt, J = 1.4, 7.3 Hz, 1 H), 7.18-7.32 (m, 6 H), 7.67-7.71 (m, 1 H);
MS m/e 406 (MH^+).

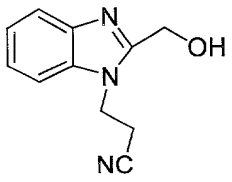


68

A mixture of lithium (30% dispersion in mineral oil, 0.5% sodium, 27 mg, 1.17 mmol) and $ZnCl_2$ (1 M, 0.58 mL, 0.58 mmol) were stirred at 0°C for 15 minutes. To this solution, *t*-butyl bromoacetate (76 mg, 0.39 mmol) was added and the resulting mixture was stirred for 15 minutes followed by addition of compound **54** (135 mg, 0.39 mmol) in THF. The mixture was stirred for an additional 15 minutes. The reaction was quenched with 1 N HCl and extracted

with EtOAc. Column chromatography (20 % EtOAc in hexanes) gave compound **68** as a brown solid:

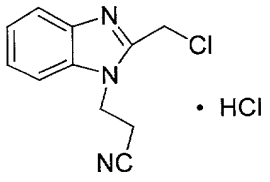
^{1}H NMR ($CDCl_3$) δ 0.99 (t, J = 6.4 Hz, 6 H), 1.35 (s, 9 H), 1.55-1.64 (m, 2 H), 1.68-1.79 (m, 1 H), 2.86 (d, J = 15.6 Hz, 1 H), 2.94 (d, J = 15.6 Hz, 1 H), 4.17-4.30 (m, 2 H), 5.04 (d, J = 15.6 Hz, 1 H), 5.34 (d, J = 15.6 Hz, 1 H), 7.05 (td, J = 0.8, 7.5 Hz, 1 H), 7.23-7.39 (m, 6 H), 7.74-7.78 (m, 1 H);
MS m/e 464 (MH^+).



69a

Compound **69a** was prepared using Michael addition conditions described by Popov, I. I. (*Khim Geterotskl. Soedin.* **1996** (6), 781-792):

^{1}H NMR ($CDCl_3$) δ 3.08 (t, J = 6.8 Hz, 2 H), 4.63 (t, J = 6.8 Hz, 2 H), 4.77 (d, J = 5.7 Hz, 2 H), 5.73 (t, J = 5.7 Hz, 1 H), 7.17-7.28 (m, 2 H), 7.64 (d, J = 1.2 Hz, 1 H), 7.70 (d, J = 1.2 Hz, 1 H);
MS m/e 202 (MH^+);
Anal. Calcd for $C_{11}H_{11}N_3O$: C 65.66; H, 5.51; N, 20.88
Found: C, 65.94; H, 5.57; N, 21.08.



69b

To a solution of alcohol **69a** (20g, 99.4 mmol) in CH_2Cl_2 (50 mL) was slowly added thionyl chloride (15.4 g, 129.2 mmol). The solution was stirred at room temperature for 3 hours. The solvent was evaporated. The residue was diluted with

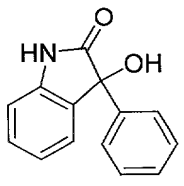
water and neutralized with saturated aqueous sodium bicarbonate solution, and extracted with EtOAc. The combined extracts were washed with water, dried over $MgSO_4$, and evaporated. The residue was triturated with Et_2O and hexane to give 19.78 g (91% yield) of compound **69b** as a white solid:

^{1}H NMR ($CDCl_3$) δ 3.02 (t, J = 7.0Hz, 2 H), 4.65 (t, J = 7.0 Hz, 2 H), 4.99 (s, 2 H), 7.34-7.44 (m, 3 H), 7.79-7.82 (m, 1 H);

MS m/e 220 (MH^+);

Anal. Calcd for $C_{11}H_{10}ClN_3$: C, 60.09; H, 4.65; N, 19.13

Found: C, 60.09; H, 4.65; N, 19.11.



69c

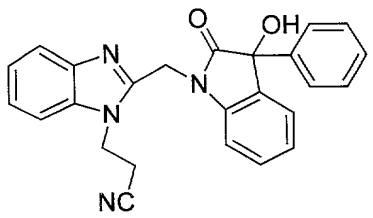
To a solution of isatin (2.94 g, 20.00 mmol) in THF (50 mL) was slowly added phenyllithium (1.8 M in hexanes, 33 mL, 60.00 mmol) at 0°C. The resulting solution was stirred at room temperature for 1 hour. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (gradient, hexanes:EtOAc = 2:1 to straight EtOAc) gave 3.55 g (79% yield) of compound **69c**:

^{1}H NMR ($CDCl_3$) δ 6.96 (d, J = 8.1 Hz, 1 H), 7.03 (t, J = 6.0 Hz, 1 H), 7.16 (t, J = 6.9 Hz, 1 H), 7.27-7.38 (m, 6 H);

MS m/e 226 (MH^+);

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22

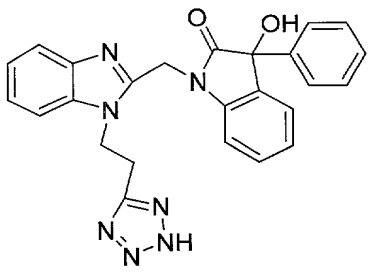
Found: C, 74.25; H, 4.99; N, 5.85.



69

A mixture of compound **69c** (371 mg, 1.65 mmol), BTPP (609 mg, 1.95 mmol), and chloride **69b** (330 mg, 1.50 mmol) were stirred together in THF (10 mL) at room temperature for 1 hour. The solvent was evaporated and the residue was diluted with water and extracted with EtOAc. The combined organic extracts were washed with water, dried over $MgSO_4$, and evaporated. Purification by flash column chromatography (gradient, EtOAc/hexanes = 2:1 to EtOAc/MeOH = 10:1) gave 540 mg (88% yield) of compound **69** as a white solid:

^{1}H NMR ($CDCl_3$) δ 2.62-2.90 (m, 2 H), 4.50-4.80 (m, 2 H), 5.12 (d, J = 16.0 Hz, 1 H), 5.47 (bd, J = 16.0 Hz, 1 H), 7.05-7.80 (m, 13 H);
IR (KBr, cm^{-1}) 3409, 2252, 1720, 1613, 1467, 1361, 1170, 746;
MS m/e 409 (MH^+).

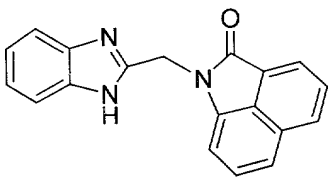


70

A mixture of compound **69** (450 mg, 1.10 mmol), sodium azide (215 mg, 3.50 mmol) and ammonium chloride (176 mg, 3.30 mmol) were stirred in DMF (15 mL) at 115 °C for 40 hours. The solvent was evaporated and the residue was diluted with 1 N NaOH and washed with Et_2O. The aqueous layer was then acidified with concentrated HCl and the solid collected by filtration. The solid was dissolved in a mixture of Et_2O and THF, dried over $MgSO_4$, and evaporated. The resulting residue was triturated in Et_2O and filtered. The solid was then

treated with 1 equivalent of 1 N NaOH in MeOH. The solvent was evaporated and the residue was triturated in Et_2O to give 258 mg (50% yield) of compound **70** as sodium salt:

^{1}H NMR (DMSO-d_6) δ 2.83-2.88 (m, 1 H), 3.10-3.15 (m, 1 H), 4.46-4.56 (m, 2 H), 5.04 (d, J = 16.5 Hz, 1 H), 5.18 (d, J = 16.5 Hz, 1 H), 6.93 (d, J = 8.0 Hz, 1 H), 6.98 (d, J = 7.3 Hz, 1 H), 7.11 (d, J = 7.5 Hz, 1 H), 7.15-7.21 (m, 6 H), 7.48 (d, J = 7.9 Hz, 2 H), 7.54 (d, J = 8.9 Hz, 2 H);
IR (KBr, cm^{-1}) 3202, 1716, 1613, 1487, 1467, 1424, 1365, 1171, 745;
MS m/e 452 (MH^+).



71a

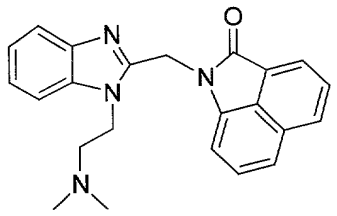
A mixture of benz[c,d]indol-2(1*H*)-one (2.00 g, 11.82 mmol) and NaH (60% suspension in mineral oil, 567 mg, 14.19 mmol) in CH_3CN (30 mL) was stirred at room temperature for 30 minutes. Compound **1b** (4.77 g, 14.19 mmol) was added and the reaction was stirred at 60°C for 72 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and evaporated to give 5.00 g of a crude mesyl protected product. The crude material was treated with excess hydrazine hydrate (20.42 g, 0.64 mol) in a mixture of MeOH and CH_2Cl_2, and the mixture was stirred at reflux for 18 hours. The solvent was evaporated and the residue was diluted with water and extracted with EtOAc. The extracts were dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (gradient, CH_2Cl_2/EtOAc, 4:1 to 1:4) gave 2 g (57% yield) of compound **71a**:

^{1}H NMR ($CDCl_3$) δ 5.39 (s, 2 H), 7.19-7.25 (m, 3 H), 7.42-7.64 (m, 5 H), 7.95-8.00 (m, 2 H);
IR (KBr, cm^{-1}) 3227, 1686, 1625, 1492, 1318, 776, 737;

MS m/e 300 (MH^+);

Anal. Calcd for $C_{19}H_{13}N_3O \bullet 0.2\ H_2O$: C, 75.33; H, 4.46; N, 13.87

Found: C, 75.57; H, 4.26; N, 13.81.



71

Compound **71a** (600 mg, 2.00 mmol) and NaH (60 % suspension in mineral oil, 240 mg, 6.00 mmol) in a mixture of toluene and DMF (30 mL, 3:1) were stirred at room temperature for 30 minutes. 2-Chloro-N,N-dimethylethylamine hydrochloride (317 mg, 2.20 mmol) was added and the reaction mixture was stirred at 55 °C for 18 hours. The reaction was diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic extracts were dried over $MgSO_4$ and evaporated. Purification by flash column chromatography (EtOAc/acetone, 3.5:1) gave 248 mg (33% yield) of compound **71**. Treatment of the free amine in MeOH with excess 4N HCl in dioxane followed by evaporation of the solvent gave the HCl salt of compound **71**:

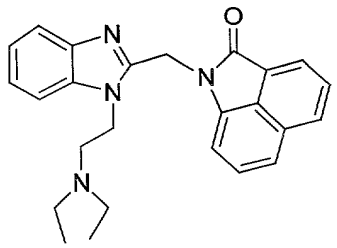
^1H NMR (CD_3OD) δ 3.14 (s, 6 H), 3.84-3.89 (m, 2 H), 5.16-5.22 (m, 2 H), 5.92 (s, 2 H), 7.43 (d, J = 7.1 Hz, 1 H), 7.60-7.74 (m, 4 H), 7.88-7.93 (m, 2 H), 8.09 (d, J = 8.1 Hz, 1 H), 8.20 (d, J = 6.9 Hz, 1 H), 8.27 (d, J = 8.1 Hz, 1 H);

IR (KBr, cm^{-1}) 3391, 1706, 1633, 1470, 1305, 964, 828, 756;

MS m/e 371 (MH^+);

Anal. Calcd for $C_{23}H_{22}N_4O \bullet 2\ HCl \bullet 3\ H_2O$: C, 55.54; H, 6.08; N, 11.26

Found: C, 55.73; H, 6.14; N, 11.03.



72

Compound **72** was prepared using the same procedure as compound **71** with 2-(diethylamino)ethyl chloride hydrochloride in 63% yield:

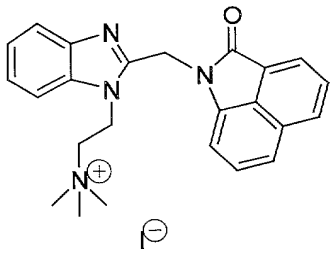
^{1}H NMR (CD_3OD) δ 1.45 (t, J = 7.3 Hz, 6 H), 3.46-3.51 (m, 4 H), 3.82 (t, J = 8.1 Hz, 2 H), 5.23 (t, J = 8.0 Hz, 2 H), 5.91 (s, 2 H), 7.42 (d, J = 7.1 Hz, 1 H), 7.59-7.78 (m, 5 H), 7.86-7.92 (m, 1 H), 8.10 (d, J = 8.2 Hz, 1 H), 8.19 (d, J = 7.0 Hz, 1 H), 8.26 (d, J = 8.2 Hz, 1 H);

IR (KBr, cm^{-1}) 3445, 2947, 1717, 1633, 1473, 1394, 1303, 966, 830, 781, 749;

MS m/e 399 (MH^+);

Anal. Calcd for $C_{25}H_{26}N_4O \bullet 2\ HCl \bullet 3\ H_2O$: C, 57.14; H, 6.52; N, 10.66

Found: C, 56.96; H, 6.48; N, 10.40.



73

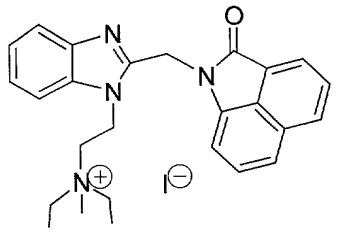
To a solution of amine **71** (50 mg, 0.14 mmol) in acetone (1.5 mL) was added methyl iodide (19 mg, 0.14 mmol). The reaction mixture was stirred under N_2 atmosphere at ambient temperature for 16 hours. The precipitate was filtered, washed with ether and dried to give 17 mg (24% yield) of compound **73**:

^{1}H NMR (CD_3OD) δ 3.43 (s, 9 H), 3.85-3.90 (m, 2 H), 5.00-5.05 (m, 2 H), 5.56 (s, 2 H), 7.33-7.42 (m, 3 H), 7.51-7.56 (m, 1 H), 7.63-7.71 (m, 3 H), 7.81-7.86 (m, 1 H), 8.14-8.20 (m, 2 H);

MS m/e 385 (MH^+).

Anal. Calcd for $C_{24}H_{25}IN_4O \bullet 0.50\ H_2O$: C, 55.29; H, 5.03; N, 10.75

Found: C, 55.10; H, 5.01; N, 10.59.



74

Compound **74** was prepared using the same procedure as compound **73** with compound **72** and methyl iodide in 49% yield:

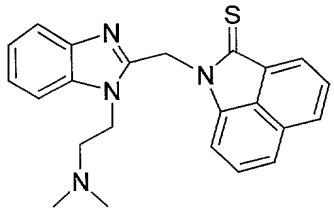
^{1}H NMR ($CDCl_3$) δ 1.44 (t, J = 7.2 Hz, 6 H), 3.31 (s, 3 H), 3.64 (q, J = 7.2 Hz, 4 H), 3.75-3.81 (m, 2 H), 4.97-5.03 (m, 2 H), 5.56 (s, 2 H), 7.31-7.43 (m, 3 H), 7.51-7.72 (m, 4 H), 7.81-7.86 (m, 1 H), 8.14-8.20 (m, 2 H);

IR (KBr, cm^{-1}) 3011, 1693, 1634, 1493, 1460, 1427, 1092, 774, 747;

MS m/e 413 (MH^+);

Anal. Calcd for $C_{26}H_{29}IN_4O$: C, 57.79; H, 5.41; N, 10.37

Found: C, 57.67; H, 5.38; N, 10.37.

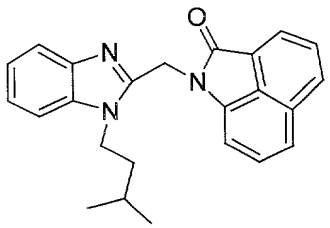


75

To a solution of compound **71** (74 mg, 0.20 mmol) in toluene (7 mL) was added 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide

(Lawesson's reagent, 51 mg, 0.13 mmol). The reaction mixture was stirred at reflux for 4 hours. The solvent was evaporated and the residue was subjected to column chromatography (gradient, straight EtOAc to EtOAc/acetone, 2:1). The product was triturated with ether and then dried *in vacuo* to give 65 mg (77% yield) of compound **75**:

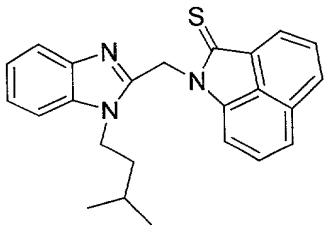
^{1}H NMR (DMSO-d_6) δ 2.20 (s, 6 H), 2.58-2.64 (m, 2 H), 4.48-4.52 (m, 2 H), 5.97 (s, 2 H), 7.11-7.16 (m, 1 H), 7.19-7.25 (m, 1 H), 7.40 (d, J = 7.2 Hz, 1 H), 7.46 (d, J = 7.9 Hz, 1 H), 7.55-7.62 (m, 2 H), 7.83 (d, J = 8.3 Hz, 1 H), 7.89 (d, J = 7.9 Hz, 1 H), 8.23 (d, J = 7.1 Hz, 1 H), 8.32 (d, J = 8.1 Hz, 1 H);
IR (KBr, cm^{-1}) 3436, 1493, 1471, 1373, 1313, 1280, 1231, 970, 818, 767, 745;
MS m/e 387 (MH^+).



76

Compound **76** was prepared using the same procedure as compound **71** with 1-bromo-3-methylbutane in 35% yield:

^{1}H NMR (CD_3OD) δ 0.92 (d, J = 6.2 Hz, 6 H), 1.65-1.69 (m, 3 H); 4.56-4.62 (m, 2 H), 5.79 (s, 2 H), 7.24 (d, J = 7.2 Hz, 1 H), 7.56-7.67 (m, 2 H), 7.71-7.77 (m, 2 H), 7.86-7.89 (m, 1 H), 7.91 (d, J = 7.1 Hz, 1 H), 8.19 (d, J = 7.0 Hz, 1 H), 8.26 (d, J = 8.1 Hz, 1 H);
IR (KBr, cm^{-1}) 3449, 2453, 1709, 1493, 1470, 1293, 831, 781, 750;
MS m/e 370 (MH^+);
Anal. Calcd for $C_{24}H_{23}N_3O \bullet HCl \bullet 1.5H_2O$: C, 66.58; H, 6.29; N, 9.71
Found: C, 66.68; H, 6.20; N, 9.53.



77

Compound **77** was prepared using the same procedure as compound **75** with compound **76**:

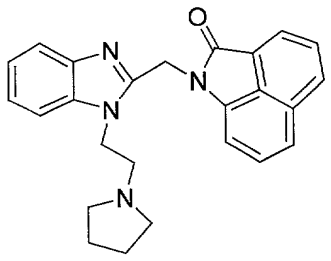
^{1}H NMR (CD_3OD) δ 0.71 (d, J = 6.6 Hz, 6 H), 1.14-1.25 (m, 2 H), 1.50-1.57 (m, 1 H), 4.22-4.28 (m, 2 H), 6.05 (s, 2 H), 7.25-7.35 (m, 2 H), 7.38 (d, J = 7.8 Hz, 1 H), 7.47 (d, J = 7.2 Hz, 1 H), 7.47 (d, J = 7.2 Hz, 1 H), 7.59 (d, J = 8.3 Hz, 1 H), 7.72 (d, J = 7.6 Hz, 1 H), 7.83-7.86 (m, 1 H), 8.05 (d, J = 8.1 Hz, 1 H), 8.28 (d, J = 7.1 Hz, 1 H);

IR (KBr, cm^{-1}) 3441, 2959, 1610, 1493, 1471, 1372, 1281, 1231, 1208, 969, 819, 744;

MS m/e 386 (MH^+);

Anal. Calcd for $C_{24}H_{23}N_3S \bullet 0.4H_2O$: C, 73.40; H, 6.11; N, 10.70

Found: C, 73.60; H, 5.83; N, 10.53.



78

Compound **78** was prepared using the same procedure as compound **71** with 1-(2-chloroethyl)pyrrolidine hydrochloride in 46% yield:

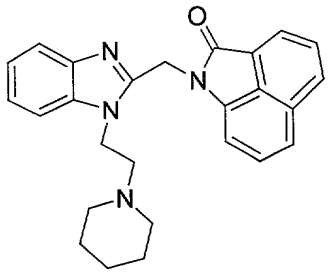
^{1}H NMR ($CDCl_3$) δ 2.26 (bs, 4 H), 3.15-3.30 (m, 2 H), 3.70-3.90 (m, 4 H), 5.39 (bs, 2 H), 6.01 (s, 2 H), 7.41 (t, J = 7.8 Hz, 1 H), 7.50-7.60 (m, 3 H), 7.69-7.79 (m, 2 H), 8.03-8.12 (m, 3 H), 8.35 (d, J = 8.3 Hz, 1 H);

IR (KBr, cm^{-1}) 3445, 2649, 1719, 1635, 1495, 1475, 1307, 969, 783, 747;

MS m/e 397 (MH^+);

Anal. Calcd for $C_{25}H_{24}N_4O \bullet 2HCl \bullet 1.5\ H_2O$: C, 60.48; H, 5.89; N, 11.28

Found: C, 60.37; H, 5.98; N, 11.19



79

Compound **79** was prepared using the same procedure as compound **71** with 1-(2-chloroethyl)piperidine monohydrochloride in 60% yield:

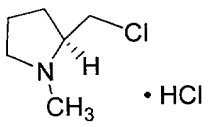
^{1}H NMR ($CDCl_3$) δ 1.07-1.37 (m, 6 H), 2.20 (bs, 4 H), 2.31 (bs, 2 H), 4.26 (bs, 2 H), 5.35 (s, 2 H), 7.09-7.33 (m, 5 H), 7.36 (dd, J = 1.2, 7.7 Hz, 1 H), 7.57 (t, J = 7.6 Hz, 1 H), 7.61-7.67 (m, 1 H), 7.87 (d, J = 8.1 Hz, 1 H), 7.95 (d, J = 7.0 Hz, 1 H);

IR (KBr, cm^{-1}) 2920, 1707, 1476, 1397, 1309, 1093, 782, 748;

MS m/e 411 (MH^+);

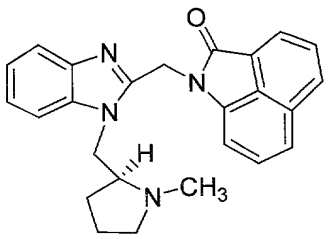
Anal. Calcd for $C_{26}H_{26}N_4O \bullet 0.3\ H_2O$: C, 75.08; H, 6.45; N, 13.47

Found: C, 75.09; H, 6.45; N, 13.45.



80a

(S)-2-(chloromethyl)-1-methylpyrrolidine hydrochloride was prepared according to the procedure reported by S. D. Kimball et al. (*J. Med. Chem.* **1992**, *35*, 780-793).



80

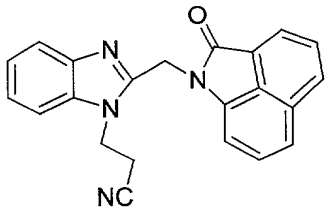
Compound **80** was prepared using the same procedure as compound **71** with compound **80a**:

^{1}H NMR (CD_3OD) δ 2.10-2.40 (m, 4 H), 3.13 (s, 3 H), 3.57-3.73 (m, 1 H), 3.85-3.95 (m, 1 H), 4.20-4.36 (m, 1H), 5.14 (dd, J = 8.9, 15.0 Hz, 1 H), 5.36 (dd, J = 5.7, 15.0 Hz, 1 H), 5.95 (s, 2 H), 7.39 (d, J = 7.1 Hz, 1 H), 7.62-7.79 (m, 5 H), 7.87-7.92 (m, 1 H), 8.10 (d, J = 9.0 Hz, 1 H), 8.19 (d, J = 6.9 Hz, 1 H), 8.26 (d, J = 8.1 Hz, 1 H);

MS m/e 397 (MH^+);

Anal. Calcd for $C_{25}H_{24}N_4O \bullet 2HCl \bullet 2H_2O$: C, 59.41; H, 5.98; N, 11.08

Found: C, 59.56; H, 5.75; N, 10.90.

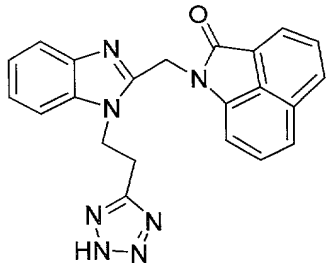


81

A mixture of compound **71a** (1.00 g, 3.34 mmol), acrylonitrile (533 mg, 10.06 mmol), and 1,3,4,6,7,8-hexahydro-1-methyl-2H-pyrimido[1,2-a] pyrimidine (MTBD, 29 mg, 0.19 mmol) in CH_3CN (35 mL) was stirred at reflux for 18 hours. The solvent was evaporated and the residue was diluted with water

and extracted with EtOAc. The organic material was dried over $MgSO_4$ and evaporated. The resulting residue was triturated with Et_2O and filtered to give 1.0 g (85% yield) of compound **81** as a yellow solid:

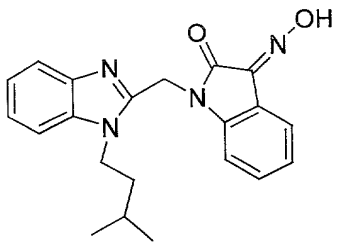
^{1}H NMR ($CDCl_3$) δ 2.72 (t, J = 6.8 Hz, 2 H), 4.75 (t, J = 6.8 Hz, 2 H), 5.50 (s, 2 H), 7.30-7.39 (m, 3 H), 7.44-7.50 (m, 2 H), 7.54-7.60 (m, 1 H), 7.75 (t, J = 8.0 Hz, 1 H), 7.81-7.85 (m, 1 H), 8.07 (d, J = 8.1 Hz, 1 H), 8.14 (d, J = 7.0 Hz, 1 H);
IR (KBr, cm^{-1}) 3363, 2247, 1686, 1633, 1466, 1395, 1363, 1095, 772, 743;
MS m/e 352 (MH^+).



82

A mixture of compound **81** (980 mg, 2.78 mmol), sodium azide (542 mg, 8.34 mmol), and ammonium chloride (446 mg, 8.34 mmol) in DMF (20 mL) was stirred at 95 °C for 72 hours. The solvent was evaporated under reduced pressure. The residue was dissolved in water and washed with EtOAc. The pH of the aqueous layer was adjusted to 7 and the yellow precipitate was collected to give 1.2 g (quantitative yield) of compound **82**:

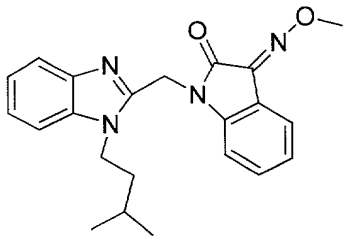
^{1}H NMR ($CDCl_3$) δ 3.41 (t, J = 6.9 Hz, 2 H), 4.83 (t, J = 6.9 Hz, 2 H), 5.25 (s, 2 H), 6.84 (d, J = 6.2 Hz, 1 H), 6.98 (d, J = 7.1 Hz, 1 H), 7.18-7.56 (m, 3 H), 7.64 (d, J = 8.5 Hz, 1 H), 7.71 (d, J = 8.1 Hz, 1 H), 7.82 (t, J = 8.0 Hz, 1 H), 8.11 (d, J = 7.0 Hz, 1 H), 8.16 (d, J = 8.1 Hz, 1 H);
IR (KBr, cm^{-1}) 3343, 1693, 1577, 1472, 1397, 775, 742;
MS m/e 396 (MH^+);
Anal. Calcd for $C_{22}H_{16}N_7O \bullet 2.7\ H_2O$: C, 56.70; H, 4.63; N, 21.04
Found: C, 56.76; H, 4.53; N, 20.88.



83

A mixture of isatin **54** (100 mg, 0.29 mmol) and hydroxylamine hydrochloride (200 mg 2.87 mmol) in MeOH (5 mL) was stirred at reflux for 1.5 hours. The solvent was evaporated and the residue was suspended in CH_2Cl_2. The filtrate was evaporated. The residue was purified by flash column chromatography (gradient, EtOAc:hexanes = 1:2 to 1:1) and the purified material was triturated with Et_2O/hexanes to give 13 mg (12% yield) of compound **83**:

^{1}H NMR (CD_3OD) δ 0.94 (d, J = 6.6 Hz, 6 H), 1.42-1.50 (m, 2 H), 1.65-1.74 (m, 1 H), 4.28-4.34 (m, 2 H), 5.32 (s, 2 H), 7.07-7.12 (m, 2 H), 7.23-7.35 (m, 3 H), 7.45 (d, J = 6.8 Hz, 1 H), 7.62 (d, J = 7.3 Hz, 1 H), 8.10 (d, J = 8.0 Hz, 1 H);
IR (KBr, cm^{-1}) 2966, 1726, 1608, 1461, 1347, 1180, 1084, 1015, 738;
MS m/e 363 (MH^+);
Anal. Calcd for $C_{21}H_{22}N_4O_2$: C, 69.59; H, 6.12; N, 15.46
Found: C, 69.22, H, 6.29; N, 15.20.

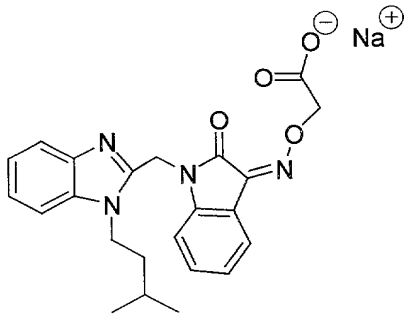


84

Compound **84** was prepared using the same procedure as compound **83** with *O*-methylhydroxylamine hydrochloride in 88% yield:

^{1}H NMR (CD_3OD) δ 0.96 (d, J = 6.6 Hz, 6 H), 1.45-1.53 (m, 2 H), 1.66-1.73 (m, 1 H), 4.30 (t over bs, 5 H), 5.30 (s, 2 H), 7.10 (d, J = 7.8 Hz, 2 H), 7.22-7.38 (m, 3 H), 7.46 (d, J = 8.4 Hz, 1 H), 7.61 (d, J = 7.2 Hz, 1 H), 7.97 (d, J = 7.5 Hz, 1 H);
IR (KBr, cm^{-1}) 3431, 2952, 1724, 1608, 1468, 1353, 1010, 752;
MS m/e 377 (MH^+);

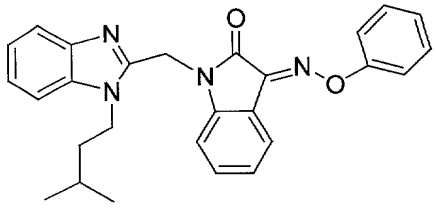
Anal. Calcd for $C_{22}H_{24}N_4O_2$: C, 70.19; H, 6.43; N, 14.88
Found: C, 69.89; H, 6.34; N, 14.80.



85

Compound **85** was prepared using the same procedure as compound **83** with carboxymethoxylamine hemihydrochloride. The sodium salt was prepared by adding 1 equivalent of 1N NaOH to the acid and evaporating the solvent:

^{1}H NMR (DMSO-d_6) δ 0.82 (d, J = 6.7 Hz, 6 H), 1.31-1.41 (m, 2 H), 1.50-1.63 (m, 1 H), 3.95-4.05 (m, 2 H), 4.83 (s, 2 H), 4.93 (s, 2 H), 6.74-6.86 (m, 1 H), 7.00-7.03 (m, 2 H), 7.03-7.05 (m, 1 H), 7.15 (bs, 2 H), 7.63-7.65 (m, 1 H), 7.84-7.89 (m, 1 H);
MS m/e 421 (MH^+).



86

Compound **86** was prepared using the same procedure as compound **83** with *O*-phenylhydroxylamine hydrochloride:

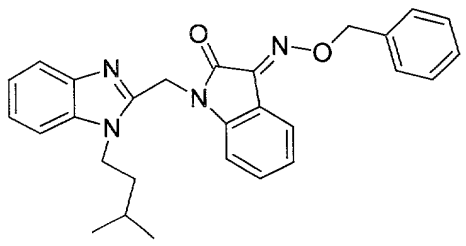
^{1}H NMR (CD_3OD) δ 0.91 (d, J = 6.5 Hz, 6 H), 1.44-1.49 (m, 2 H), 1.65-1.69 (m, 1 H), 4.30 (t, J = 8.3 Hz, 5 H), 5.32 (s, 2 H), 5.52 (s, 2 H), 7.07-7.09 (m, 2 H), 7.24-7.41 (m, 6 H), 7.45-7.50 (m, 3 H), 7.61 (d, J = 7.4 Hz, 1 H), 7.96 (d, J = 7.6 Hz, 1 H);

IR (KBr, cm^{-1}) 3443, 2951, 1731, 1607, 1467, 1372, 1332, 979, 744;

MS m/e 453 (MH^+);

Anal. Calcd for $C_{22}H_{24}N_4O_2$: C, 74.31; H, 6.24; N, 12.38

Found: C, 74.02; H, 6.14; N, 12.36.



87

Compound **87** was prepared using the same procedure as compound **83** with *O*-benzylhydroxylamine hydrochloride in 78% yield:

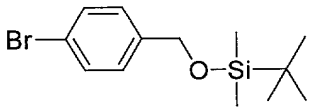
^{1}H NMR (CD_3OD) δ 0.91 (d, J = 6.5 Hz, 6 H), 1.44-1.49 (m, 2 H), 1.65-1.69 (m, 1 H), 4.30 (t, J = 8.3 Hz, 5 H), 5.32 (s, 2 H), 5.52 (s, 2 H), 7.07-7.09 (m, 2 H), 7.24-7.41 (m, 6 H), 7.45-7.50 (m, 3 H), 7.61 (d, J = 7.4 Hz, 1 H), 7.96 (d, J = 7.6 Hz, 1 H);

IR (KBr, cm^{-1}) 3443, 2951, 1731, 1607, 1467, 1372, 1332, 979, 744;

MS m/e 453 (MH^+);

Anal. Calcd for $C_{22}H_{24}N_4O_2$: C, 74.31; H, 6.24; N, 12.38

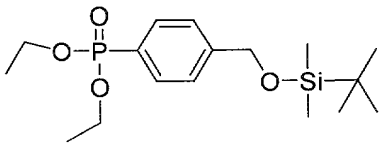
Found: C, 74.02; H, 6.14; N, 12.36.



88a

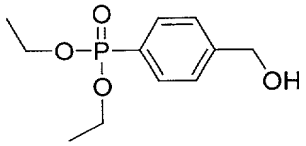
To a solution of 4-bromobenzyl alcohol (56.8 g, 0.304 mol) and imidazole (31.0 g, 0.456 mol) in THF (500 ml) at 0 °C was added TBDMS chloride (50.3 g, 0.334 mol) in one portion. After stirring at room temperature for 1 hour, the suspension was filtered. The filtrate was diluted with EtOAc (500 ml), washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was distilled under vacuum to provide 84.6 g (92% yield) of compound **88a** as a colorless oil:

^1H NMR ($CDCl_3$) δ 0.95 (s, 9 H), 4.69 (s, 2 H), 7.21 (d, J = 7.5 Hz, 2 H), 7.44 (d, J = 7.5 Hz, 2 H);
MS m/e 282 (MH^+).



88b

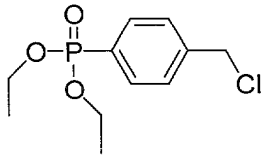
To a solution of bromide **88a** (73.0 g, 0.242 mol) in THF (500 ml) at –78 °C was added *t*-BuLi (1.7 M in heptane, 314 ml, 0.533 mol) dropwise. The mixture was stirred at –78 °C for 30 minutes before addition of diethyl chlorophosphate (43.9 g, 0.254 mol). The reaction mixture was stirred for 2 hours and was quenched with saturated NH_4Cl. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude product **88b** was used for the next reaction without further purification.



88c

To a solution of compound **88b** (31.1 g, 86.8 mmol) in THF (300 ml) at 0 °C was added TBAF (1M in THF, 104 ml, 104 mmol). The reaction mixture was stirred for 2 hours and was quenched with saturated NH_4Cl . The organic layer was diluted with EtOAc (300 ml), washed with water and brine, dried over $MgSO_4$, and concentrated. The crude alcohol product **88c** was used for the next reaction without further purification:

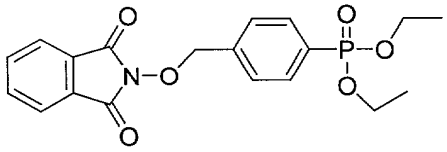
^1H NMR ($CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 6 H), 4.00-4.11 (m, 4 H), 4.71 (s, 2 H), 7.42 (dd, J = 3.6, 8.0 Hz, 2 H), 7.70 (dd, J = 8.0, 12.9 Hz, 2 H).



88d

Chloride **88d** was prepared using the same procedure as compound **4c** with compound **88c** and thionyl chloride:

^1H NMR ($CDCl_3$) δ 1.31 (t, J = 7.2 Hz, 6 H), 4.05-4.16 (m, 4 H), 4.59 (s, 2 H), 7.48 (dd, J = 3.9, 8.0 Hz, 2 H), 7.80 (dd, J = 8.0, 13.2 Hz, 2 H);
MS m/e 262 (MH^+).

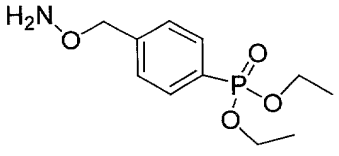


88e

A mixture of N-hydroxyphthalimide (0.90 g, 5.5 mmol), compound **88d** (1.32 g, 5.0 mmol), and DIEA (1.26 g, 10 mmol) in CH_3CN (50 ml) was stirred at reflux for 4 hours. The resulting solution was diluted with CH_2Cl_2 (100 mL) and washed with saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (gradient,

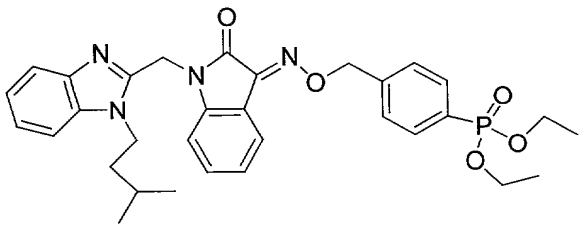
CH_2Cl_2:MeOH = 40:1 to 30:1) to give 1.39 g (65% yield) of compound **88e** as a viscous oil:

^1H NMR (CD_3OD) δ 1.28-1.33 (m, 6 H), 4.08-4.13 (m, 4 H), 5.25 (s, 2 H), 7.47-7.50 (m, 2 H), 7.77-7.82 (m, 8 H);
MS m/e 390 (MH^+).



88f

A solution of compound **88e** (1.50 g, 3.85 mmol) and hydrazine (0.33 g, 9.6 mmol) in MeOH (50 ml) was stirred at reflux for 12 hours. The mixture was filtered and the filtrate was concentrated. Trituration of the residue with hot $CHCl_3$ (50 ml), followed by filtration and concentration of the filtrate gave 0.90 g (90% yield) of compound **88f** as a viscous oil, which was used without further purification.



88

A mixture of compound **54** (902 mg, 2.60 mmol), compound **88f** (808 mg, 3.12 mmol) and *p*-toluenesulphonic acid (99 mg, 0.52 mmol) in MeOH (26 ml) was stirred at reflux for 1 hour. The reaction mixture was diluted with CH_2Cl_2 (100 ml), washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (gradient, CH_2Cl_2:MeOH = 40:1 to 20:1) to give 1.29 g (84% yield) of compound **88** as a yellow foam:

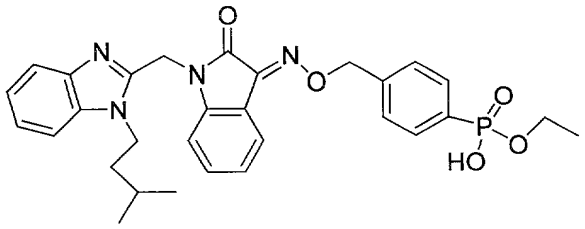
^{1}H NMR (CD_3OD) δ 0.91 (d, J = 6.6 Hz, 6 H), 1.34 (t, J = 7.2 Hz, 6 H), 1.46-1.54 (m, 2 H), 1.64-1.71 (m, 1 H), 4.07-4.30 (m, 4 H), 4.32 (t, J = 8.2 Hz, 2 H), 5.33 (s, 2 H), 5.62 (s, 2 H), 7.09-7.16 (m, 2 H), 7.26-7.37 (m, 2 H), 7.39-7.42 (m, 1 H), 7.48-7.50 (m, 1 H), 7.62-7.70 (m, 3 H), 7.79-7.84 (m, 2 H), 8.04-8.07 (m, 1 H);

IR (KBr, cm^{-1}) 3436, 2957, 1727, 1607, 1468, 1023;

MS m/e 588 (MH^+);

Anal. Calcd for $C_{32}H_{37}N_4O_5P \bullet H_2O$: C, 63.36; H, 6.48; N, 9.24

Found: C, 63.34; H, 6.48; N, 9.15.



89

Compound **88** (294 mg, 0.5 mmol) and 1 N NaOH (1.50 ml, 1.50 mmol) in a mixture of MeOH and H_2O (20 ml, 1:1) was heated to reflux for 12 hours. The mixture was acidified with 1 N HCl to pH 2 and concentrated. The residue was purified by prep-HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 360 mg (56% yield) of compound **89** as a yellow gel:

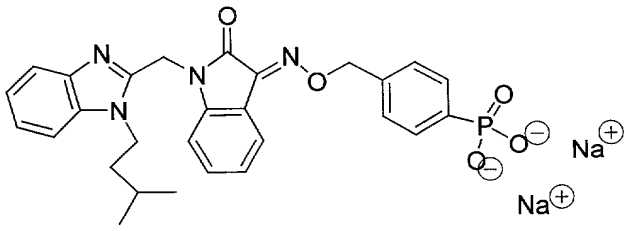
^{1}H NMR (CD_3OD) δ 0.94 (d, J = 6.6 Hz, 6 H), 1.19 (t, J = 7.1 Hz, 3 H), 1.46-1.53 (m, 2 H), 1.66-1.75 (m, 1 H), 3.76-3.86 (m, 2 H), 4.33 (t, J = 8.3 Hz, 2 H), 5.34 (s, 2 H), 5.57 (s, 2 H), 7.08-7.13 (m, 2 H), 7.25-7.40 (m, 3 H), 7.47-7.55 (m, 3 H), 7.64 (d, J = 7.3 Hz, 1 H), 7.80-7.87 (m, 2 H), 8.00-8.03 (m, 1 H);

IR (KBr, cm^{-1}) 3436, 2959, 1684, 1210, 1135;

MS m/e 561 (MH^+);

Anal. Calcd for $C_{30}H_{33}N_4O_5P \bullet 4H_2O \bullet 0.5TFA$: C, 52.32; H, 5.74; N, 7.87

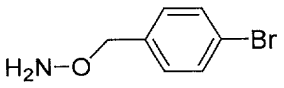
Found: C, 52.66; H, 5.66; N, 7.94.



90

To a solution of compound **88** (720 mg, 1.22 mmol) in CH_3CN (25 ml) at 0°C was added TMS bromide (1.86 g, 12.2 mmol) and stirred at room temperature for 12 hours. The mixture was concentrated and the residue was purified by preperative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 474 mg (73% yield) yellow powder. To a mixture of this yellow solid (60 mg, 0.11 mmol) in MeOH (2 ml) and H_2O (1 ml) was added 1N NaOH (0.225 ml, 0.22 mmol). The solution was concentrated and the residue was triturated with hot EtOAc to give 59 mg (90%) of compound **90** as yellow solid:

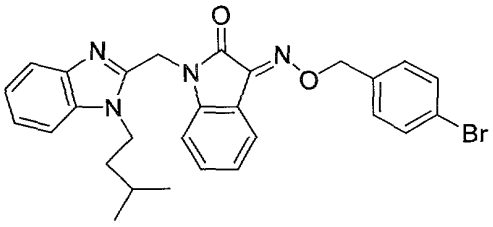
^{1}H NMR (CD_3OD) δ 0.98 (d, J = 6.6 Hz, 6 H), 1.48-1.55 (m, 2 H), 1.68-1.77 (m, 1 H), 4.34 (t, J = 8.2 Hz, 2 H), 5.34 (s, 2 H), 5.53 (s, 2 H), 7.04-7.14 (m, 2 H), 7.25-7.39 (m, 3 H), 7.42-7.50 (m, 3 H), 7.63-7.66 (m, 1 H), 7.90-7.96 (m, 3 H);
IR (KBr, cm^{-1}) 3392, 2953, 1721, 1611, 1469, 970;
MS m/e 533 (MH^+);
Anal. Calcd for $C_{28}H_{27}N_4Na_2O_5P \bullet 4H_2O \bullet 0.5TFA$: C, 49.37; H, 5.07; N, 7.94
Found: C, 49.50; H, 5.47; N, 7.98.



91a

Compound **91a** was prepared using the same procedure sequence as compound **88f** starting with 4-bromobenzyl bromide:

^{1}H NMR (DMSO-d_6) δ 6.09 (s, 2 H), 7.27-7.30 (m, 2 H), 7.52-7.55 (m, 2 H);
MS m/e 203, 205 (MH^+).



92

Compound **92** was prepared using the same procedure as compound **88** with compound **91a**:

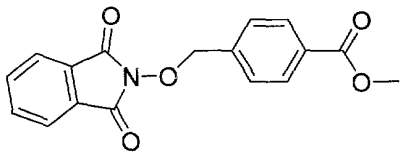
^{1}H NMR (DMSO-d_6) δ 0.92 (d, J = 6.6 Hz, 6 H), 1.55-1.59 (m, 2 H), 1.66-1.69 (m, 1 H), 4.38 (t, J = 7.7 Hz, 2 H), 5.42 (s, 2 H), 5.51 (s, 2 H), 7.13-7.20 (m, 2 H), 7.32-7.44 (m, 2 H), 7.45-7.47 (m, 3 H), 7.60-7.66 (m, 3 H), 7.70-7.71 (m, 1 H), 7.97 (d, J = 7.2 Hz, 1 H);

IR (KBr, cm^{-1}) 3445, 2956, 1727, 1607, 1468, 976;

MS m/e 531, 533 (MH^+);

Anal. Calcd for $C_{28}H_{27}BrN_4O_2$: C, 63.28; H, 5.12; N, 10.54

Found: C, 63.03; H, 5.14; N, 10.48.

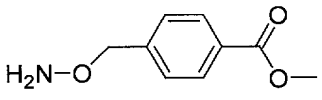


93a

Compound **93a** was prepared using the same sequence of procedures as compound **88e** starting with methyl 4-(bromomethyl)-benzoate:

^{1}H NMR ($CDCl_3$) δ 3.94 (s, 2 H), 5.29 (s, 2 H), 7.64 (d, J = 8.2 Hz, 2 H), 7.75-7.85 (m, 4 H), 8.08 (d, J = 8.2 Hz, 2 H);

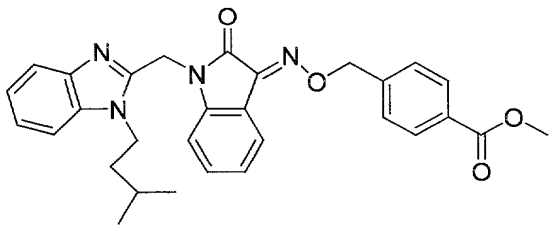
MS m/e 312 (MH^+).



93b

Compound **93b** was prepared using the same procedure as compound **88f** with compound **93a**:

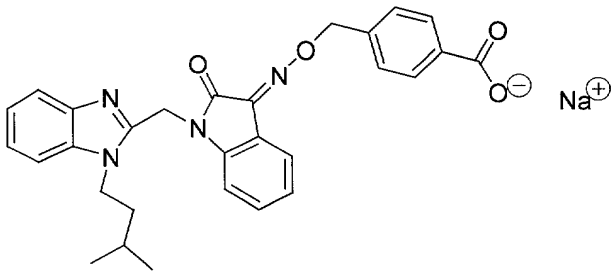
^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3 H), 4.75 (s, 2 H), 5.48 (bs, 2 H), 7.43 (d, J = 8.3 Hz, 2 H), 8.03 (d, J = 8.3 Hz, 2 H);
MS m/e 182 (MH^+).



93

Compound **93** was prepared using the same procedure as compound **88** with compound **93b**:

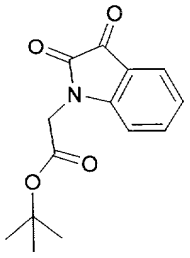
^{1}H NMR (DMSO-d_6) δ 0.89 (d, J = 6.6 Hz, 6 H), 1.40-1.70 (m, 3 H), 3.86 (s, 3 H), 4.25-4.30 (m, 2 H), 5.27 (s, 2 H), 5.62 (s, 2 H), 7.10-7.27 (m, 3 H), 7.43-7.62 (m, 6 H), 7.97-8.02 (m, 3 H);
MS m/e 511 (MH^+);
Anal. Calcd for $C_{30}H_{30}N_4O_4 \bullet 0.25H_2O$: C, 69.95; H, 5.97; N, 10.88
Found: C, 69.59; H, 5.68; N, 10.69.



94

Compound **93** (81 mg, 0.13 mmol) and 1N NaOH (0.39 mL, 0.39 mmol) were stirred at reflux in MeOH (5 mL). The solvent was evaporated and the residue was diluted with water. The aqueous material was adjusted to neutral pH with 1N HCl and extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and evaporated. The resulting acid was stirred with exactly 1 equivalent of 1N NaOH in MeOH and then the solvent was evaporated to give 24 mg (36% yield) of the sodium salt **94**:

^{1}H NMR (DMSO-d_6) δ 0.89 (d, J = 6.5 Hz, 6 H), 1.42-1.66 (m, 3 H), 4.26 (bt, J = 8.1 Hz, 2 H), 5.26 (s, 2 H), 5.60 (s, 2 H), 7.09-7.52 (m, 8 H), 7.58 (d, J = 8.1 Hz, 2 H), 7.98 (d, J = 8.1 Hz, 2 H);
MS m/e 497 (MH^+).

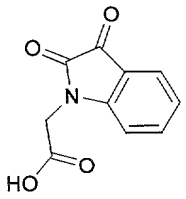


95a

A solution of isatin (10 g, 68 mmol) and *t*-butyl bromoacetate (10 mL, 68 mmol) and K_2CO_3 (18.8 g, 136 mmol) in CH_3CN (50 mL) was heated to reflux for 3 hours then cooled, filtered and concentrated. The residue was purified by flash chromatography (heaxanes:EtOAc = 9:1) to give 8.38 g (47% yield) of compound **95a** as an orange solid:

^{1}H NMR (DMSO-d_6) δ 1.41 (s, 9 H), 4.50 (s, 2 H), 7.17 (t, J = 8.4 Hz, 2 H), 7.60 (d, J = 8.5 Hz, 1 H), 7.68 (t, J = 8.4 Hz, 1 H);
MS m/e 261 (MH^+);

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36
Found: C, 64.41; H, 5.96; N, 5.28.

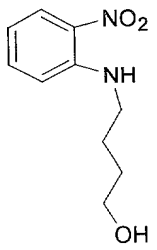


95b

A mixture of ester **95a** (5.0 g, 19.10 mmol) and TFA (20 mL) was stirred at room temperature for 12 hours. The solvent was removed and the residue was dried under vacuum to give 3.5 g (77% yield) of compound **95b** as an orange solid:

^{1}H NMR (DMSO-d_6) δ 4.50 (s, 2 H), 7.15-7.20 (m, 2 H), 7.60 (d, J = 8.5 Hz, 1 H), 7.68 (t, J = 8.4 Hz, 1 H);

MS m/e 205 (MH^+).



95c

A solution of 2-fluoronitrobenzene (5.0 g, 35.50 mmol) and 1-amino-4-butanol (3.2 g, 35.50 mmol) in CH_3CN (100 mL) and triethylamine (4.0 g, 35.5 mmol) was heated to reflux for 12 hours, then cooled and concentrated. The residue was dissolved in EtOAc and washed with 1N HCl. The mixture was dried over $MgSO_4$ and concentrated to give 7.21 g (97% yield) of compound **95c** as a dark orange solid:

^{1}H NMR (DMSO-d_6) δ 1.45-1.56 (m, 2 H), 1.58-1.69 (2 H), 3.35 (t, J = 6.7 Hz, 2 H coupled to proton exchangeable in D_2O), 3.43 (t, J = 6.4 Hz, 2 H), 3.90-4.00 (br, 1 H, exchanges with D_2O), 6.66 (t, J = 6.0 Hz, 1 H), 7.04 (d, J = 9.0 Hz, 1 H),

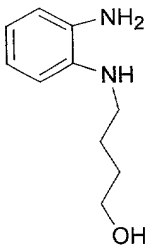
7.52 (t, J = 7.2 Hz, 1 H), 8.04 (d, J = 1.6, 7.2 Hz, 1 H), 8.13 (bs, 1 H, exchanges with D_2O, 1 H);

IR (KBr cm^{-1}) 1350, 1154;

MS m/e 211 (MH^+);

Anal. Calcd for $C_{10}H_{14}N_2O_3 \cdot 0.28\ H_2O$: C, 55.80; H, 6.82; N, 13.01

Found: C, 55.80; H, 6.62; N, 12.97.



95d

A solution of the nitro compound **95c** (5.0 g, 23.80 mmol) in ethanol (50 mL) was hydrogenated at 40 psi with 10% palladium on carbon (100 mg) for 4 hours. The catalyst was removed by filtration and the solvent was evaporated to give 4.3 g (99% yield) of compound **95d** as a dark oil:

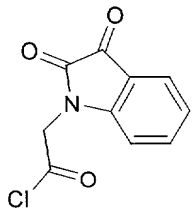
^1H NMR (DMSO-d_6) δ 1.47-1.66 (m, 4 H), 2.99 (t, J = 6.6 Hz, 2 H), 3.43 (t, J = 6.6 Hz, 2 H), 4.31-4.50 (br, exchange with D_2O, 4 H), 6.36-6.42 (m, 2 H) 6.54-6.82 (m, 2 H);

IR (film cm^{-1}) 1055, 739;

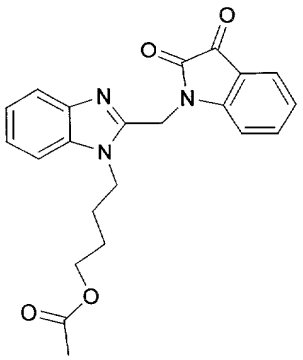
MS m/e 181 (MH^+);

Anal. Calcd for $C_{10}H_{16}N_2O \cdot 0.71\ H_2O$: C, 62.23; H, 9.10; N, 14.51

Found: C, 62.23; H, 8.78; N, 14.41.



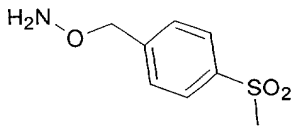
95e



95

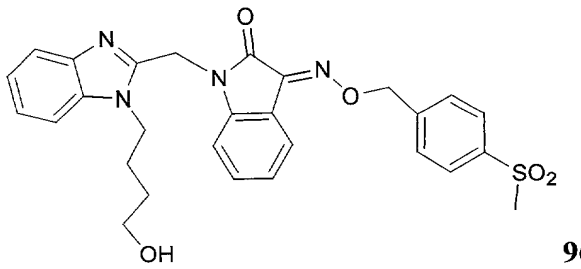
To a solution of compound **95d** (4.97 g, 27.60 mmol) and triethylamine (3.0 g, 30 mmol) in CH_2Cl_2 (100 mL) at -78°C was added compound **95e** (freshly prepared from compound **95b** (5.66g, 27.60 mmol) and oxalyl chloride (3.5 g, 27.60 mmol)) in CH_2Cl_2 (50 mL). The mixture was stirred at -78°C for 1 hour then warmed to room temperature and stirred for 12 hours. The solvent was removed. The residue was dissolved in AcOH (100 mL) and heated to reflux for 12 hours. The solvent was evaporated and the residue was purifed by flash chromatography (hexanes:EtOAc = 3:1) to give 2.2 g (20% yield) of compound **95** as a yellow solid:

^{1}H NMR (DMSO-d_6) δ 1.63-1.66 (m, 2 H), 1.77-1.81 (m, 2 H), 1.90 (s, 3 H), 1.99 (s, 3 H), 4.03 (t, J = 6.6 Hz, 2 H), 4.34 (t, J = 7.5 Hz, 2 H), 5.24 (s, 2 H), 7.14-7.19 (m, 2 H), 7.25 (t, J = 8.2 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 7.58-7.67 (m, 4 H);
MS m/e 391 (MH^+).



96a

Compound **96a** was prepared using the same procedure sequence as compound **88f** starting with *p*-methylsulfonylbenzyl chloride.



96

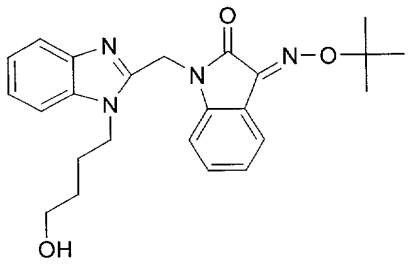
A mixture of compound **95** (0.39 g, 0.99 mmol) and **96a** (0.2 g, 0.99 mmol) in EtOH (50 mL) was heated to reflux for 12 hours. The solution was concentrated and filtered to give 195 mg (34% yield) of intermediate as a yellow solid. The solid was dissolved in MeOH (50 mL) and treated with *p*-toluenesulfonic acid (0.21 g, 1.10 mmol) and stirred at reflux for 12 hours. The mixture was cooled, concentrated. The residue was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated. The residue was dissolved in a minimum of MeOH and diluted with water. After standing for 1 hour, the precipitated product was isolated by filtration to give 0.12 g (66% yield) of compound **96** as a yellow solid:

^{1}H NMR (DMSO-d_6) δ 1.40-1.55 (m, 2 H), 1.70-1.80 (m, 2 H), 3.19 (s, 3 H), 3.38-3.99 (m, 2 H), 4.31-4.33 (m, 2 H), 5.26 (s, 2 H), 5.65 (s, 2 H), 7.11-7.24 (m, 4 H), 7.45 (t, J = 7.8 Hz, 1 H), 7.55 (t, J = 6.8 Hz, 2 H), 7.73 (d, J = 7.6 Hz, 2 H), 7.98 (d, J = 8.2 Hz, 2 H), 7.90-8.00 (m, 1 H);

MS m/e 532 (MH^+);

Anal. Calcd for $C_{28}H_{28}N_4O_5 \bullet 0.6\ H_2O$: C, 61.89; H, 5.42; N, 10.31

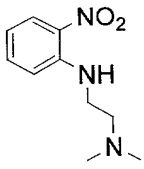
Found: C, 61.93; H, 5.23; N, 10.33.



97

Compound **97** was prepared using the same procedure as compound **96** with *O*-(*tert*-butyl)hydroxylamine hydrochloride:

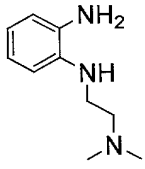
^{1}H NMR (DMSO-d_6) δ 1.15 (s, 9 H), 1.45-1.48 (m, 2 H), 1.75-1.80 (m, 2 H), 3.40 (t, J = 6.2 Hz, 2 H), 4.29 (t, J = 7.6 Hz, 2 H), 4.52 (d, J = 5.3 Hz, 2 H), 4.85-4.96 (bs, 1 H), 6.55-6.61 (m, 1 H), 6.84-6.87 (m, 1 H); 7.04-7.07 (m, 2 H), 7.17-7.21 (m, 2 H), 7.54 (d, J = 7.9 Hz, 1 H), 7.61 (d, J = 7.7 Hz, 1 H);
MS m/e 421 (MH^+).



98a

To a mixture of 2-fluoronitrobenzene (16.8 g, 119 mmol) and sodium acetate (300 mg) was added N,N-dimethylethylenediamine (12.5 mL, 113 mmol). After heating to 80 °C for 1 hour, the mixture was poured into water, and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and evaporated. The crude material was purified by silica gel chromatography (gradient, 1:1 EtOAc:Hexanes to 5% MeOH in EtOAc) to provide 12.0 g (50% yield) of compound **98a** as an orange oil:

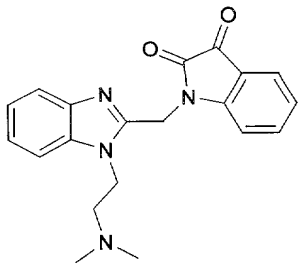
^{1}H NMR ($CDCl_3$) δ 2.30 (s, 6 H), 2.63 (t, J = 6.3 Hz, 2 H), 3.33-3.37 (m, 2 H), 6.63 (t, J = 8.3 Hz, 1 H), 6.82 (d, J = 8.3 Hz, 1 H), 7.43 (t, J = 8.1 Hz, 1 H), 8.17 (d, J = 8.5 Hz, 1 H), 8.33 (bs, 1 H);
MS m/e 209 (MH^+).



98b

A mixture of compound **98a** (10.0 g, 47.7 mmol) and 10% palladium on carbon (500 mg) in EtOH (100 mL) was hydrogenated at 50 psi for 1 hour. The mixture was filtered through a pad of celite and the filtrate was evaporated. The residue was recrystallized from hexanes to give 7.52 g (88% yield) of compound **98b** as flaky brown solid:

^{1}H NMR ($CDCl_3$) δ 2.26 (s, 6 H), 2.60 (t, J = 6.1 Hz, 2 H), 3.33-3.37 (t, J = 6.1 Hz, 2 H), 6.65-6.72 (m, 3H), 6.81 (t, J = 7.5 Hz, 1H);
MS m/e 179 (MH^+).

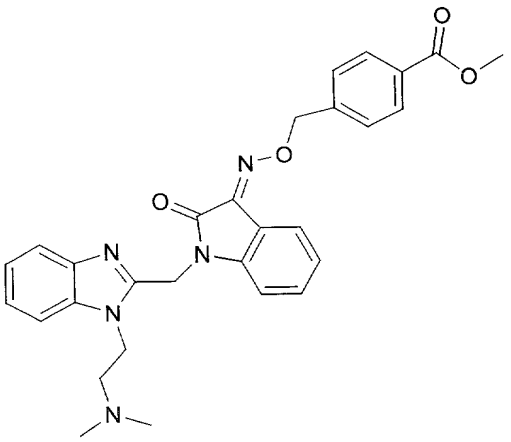


98

To a solution of compound **98b** (2.6 g, 14.6 mmol) in CH_2Cl_2 (50 mL) at –78 °C was added compound **95e** (freshly prepared from **95b** (3.0g, 14.6 mmol) and thionyl chloride, 20 mL) in CH_2Cl_2 (50 mL). The mixture was stirred at –78 °C for 1 hour then warmed to room temperature and stirred for 12 hours. The solvent was removed to give 2.8 g of a mixture of mono and diacetylated products. Both compounds can be converted to the desired product by heating the mixture in AcOH (100 mL) and concentrated HCl (2 mL) at reflux for 12 hours. The residue was purified by flash chromatography (gradient, CH_2Cl_2:MeOH = 99:1 to CH_2Cl_2:MeOH = 97:3) to give 1.8 g (68% yield) of compound **98** as a yellow solid:

^{1}H NMR (DMSO-d_6) δ 2.11 (s, 6 H), 2.58 (t, J = 6.0 Hz, 2 H), 4.39 (t, J = 6.0 Hz, 2 H), 5.27 (s, 2 H), 7.11-7.26 (m, 4 H), 7.54-7.65 (m, 4 H);
MS m/e 348 (MH^+);
Anal. Calcd for $C_{20}H_{20}N_4O_2 \bullet 0.7\ H_2O \bullet 0.5$ AcOH: C, 64.50; H, 6.03; N, 14.33

Found: C, 64.68; H, 5.93; N, 14.32.



99

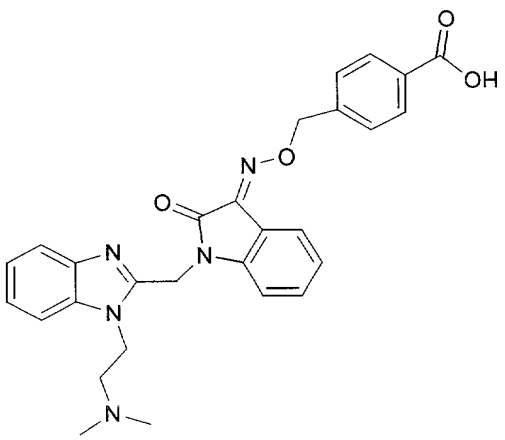
A mixture of compound **98** (200 mg, 0.57 mmol), compound **93b** (104 mg, 0.57 mmol) and *p*-toluenesulfonic acid (162 mg, 0.87 mmol) was stirred at reflux for 12 hours. The mixture was concentrated and the residue dissolved in EtOAc, washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. The dark residue was purified by preparative HPLC (gradient, 80%MeOH/water to 100% MeOH/water) to give 128 mg (44% yield) of compound **99** as a dark oil:

^{1}H NMR (DMSO-d_6) δ 2.95 (s, 6 H), 3.50-3.70 (m, 2 H), 3.86 (s, 3 H), 4.72-4.77 (m, 2 H), 3.38 (s, 2 H), 5.62 (s, 2 H), 7.10-7.27 (m, 4 H), 7.44-7.49 (m, 1 H), 7.58-7.63 (m, 3 H), 7.63-7.69 (d, J = 8.0 Hz, 1 H), 7.98-8.03 (m, 3 H);

MS m/e 511 (MH^+);

Anal. Calcd for $C_{29}H_{29}N_5O_4 \bullet 0.4\ H_2O$: C, 46.29; H, 3.56; N, 7.38

Found: C, 46.29; H, 3.72; N, 7.49.



100

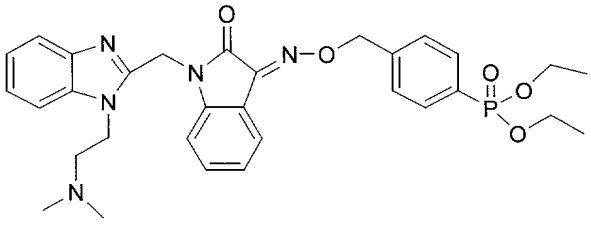
A solution of compound **99** in aqueous 1N HCl (50 mL) was heated to reflux for 6 hours then cooled and concentrated. The residue was purified by preparative HPLC (C18, gradient, 50-70%MeOH/water) to give a yellow solid. The solid was dissolved in 4N HCl in dioxane (10 mL). The solvent and excess HCl were evaporated to give 95 mg (75% yield) of compound **100** as a hydrochloride salt:

^{1}H NMR (DMSO-d_6) δ 2.90 (s, 6 H), 3.60-3.70 (m, 2 H), 5.00-5.03 (m, 2 H), 5.62 (s, 2 H), 5.66 (s, 2 H), 7.18 (t, J = 7.6 Hz, 1 H), 7.9 (d, J = 7.9 Hz, 1 H), 7.44-7.54 (m, 3 H), 7.60 (d, J = 8.2 Hz, 2 H), 7.69 (d, J = 8.0 Hz, 1 H), 7.99-8.03 (m, 3 H), 8.10 (d, J = 8.2 Hz, 1 H);

MS m/e 497 (MH^+);

Anal. Calcd for $C_{28}H_{27}N_5O_4 \bullet 2.9\ H_2O \bullet 1.8$ HCl: C, 54.74; H, 5.67, N, 11.40

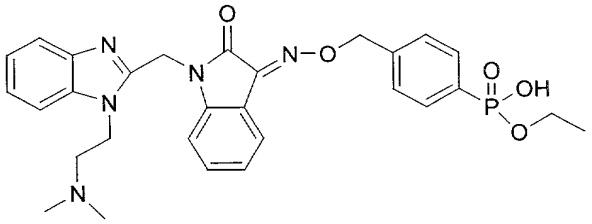
Found: C, 54.98; H, 5.27; N, 11.00.



101

Compound **101** was prepared using the same method as compound **99** with compound **88f**:

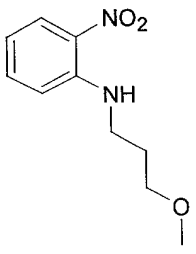
^{1}H NMR (DMSO-d_6) δ 1.23 (t, J = 7.0 Hz, 6 H), 2.91 (d, J = 4.8 Hz, 6 H), 3.57 (s, 2 H), 3.97-4.04 (m, 4 H), 4.86 (t, J = 7.4 Hz, 2 H), 5.47 (s, 2 H),.5.62 (s, 2 H), 7.17 (t, J = 7.7 Hz, 1 H), 7.25 (d, J = 8.0 Hz, 1 H), 7.30 (t, J = 7.7 Hz, 1 H), 7.39 (t, J = 7.4 Hz, 1 H), 7.45-7.49 (m, 1 H), 7.59-7.65 (m, 3 H), 7.72-7.80 (m, 2 H), 7.86 (d, J = 7.9 Hz, 1 H), 8.01 (t, J = 7.7 Hz, 1 H);
MS m/e 590 (MH^+).



102

Compound **102** was prepared using the same procedure as compound **89** with compound **101**:

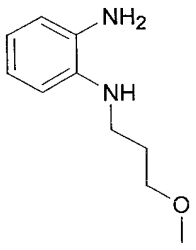
^{1}H NMR (DMSO-d_6) δ 1.09 (t, J = 7.0 Hz, 3 H), 3.00-3.10 (m, 2 H), 3.38 (bs, 6 H), 3.71-3.77 (m, 2 H), 4.55-4.70 (m, 2 H), 5.27 (s, 2 H), 5.50 (s, 2 H), 7.10 (t, J = 7.6 Hz, 1 H), 7.11-7.21 (m, 2 H), 7.23 (t, J = 7.1 Hz, 1 H), 7.40 (t, J = 6.7 Hz, 1 H), 7.41-7.47 (m, 2 H), 7.54 (d, J = 8.0 Hz, 1 H), 7.63 (d, J = 8.1 Hz, 1 H), 7.68-7.72 (m, 2 H), 7.92 (d, J = 6.9 Hz, 1 H).



103a

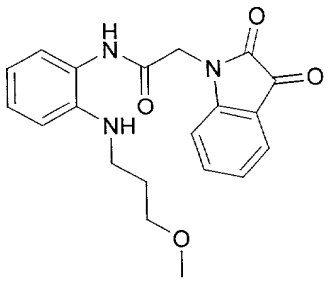
To a mixture of 2-methoxypropylamine (8.45 g, 94.83 mmol) and potassium carbonate (26.21 g, 189.66 mmol) in CH_2Cl_2 (150 mL) was added 1-fluoro-2-nitrobenzene (13.38 g, 94.83 mmol) dropwise. The resulting mixture was stirred at 65 °C for 20 hours. The potassium carbonate was removed by filtration. The filtrate was washed with water and saturated aqueous sodium chloride, dried over $MgSO_4$, and evaporated to give 19.6 g (98% yield) of intermediate **103a** as an orange oil:

^{1}H NMR ($CDCl_3$) δ 1.95-2.00 (m, 2 H), 3.37 (s, 3 H), 3.39-3.43 (m, 2 H), 3.52 (t, J = 5.7 Hz, 2 H), 6.60 (dt, J = 1.2, 8.0 Hz, 1 H), 6.85 (d, J = 1.4, 7.0 Hz, 1 H), 8.14 (dd, J = 1.4, 7.0 Hz, 1 H), 8.28 (bs, 1 H).



103b

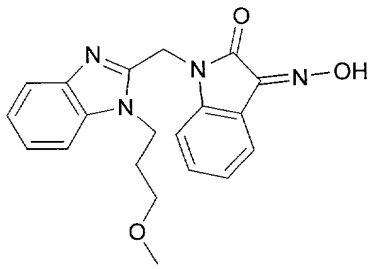
A mixture of **103a** (5.87 g, 27.92 mmol) and 10% palladium on carbon (1.17 g) in MeOH (100 mL) was hydrogenated at 50 psi for 4 hours. The catalyst was removed by filtration through a pad of celite. The filtrate was evaporated to give 4.59 g (91% yield) of the diamine **103b**.



103c

To a mixture of diamine **103b** (3.45 g, 19.14 mmol) and DIEA (4.95 g, 38.30 mmol) in anhydrous THF (75 mL) was added a solution of compound **95e**

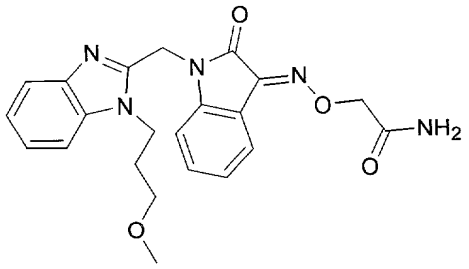
(4.28 g, 19.14 mmol) in THF (50 mL) slowly over 15 minutes. The resulting mixture was stirred for 10 minutes at room temperature. The solvent was evaporated to give the intermediate **103c** which was used without further purification.



104

A mixture of compound **103c** (7.00 g, 19.0 mmol) and hydroxylamine hydrochloride (1.46 g, 21.0 mmol) in glacial acetic acid (150mL) was stirred at 120 °C for 30 minutes. The mixture was then concentrated *in vacuo* to a yellow solid. The crude solid was triturated with cold CH_2Cl_2 and isolated by filtration. The solid was redissolved in EtOAc and washed three times with saturated aqueous $NaHCO_3$ and then with brine. The organic phase was dried over anhydrous Na_2SO_4 and partially concentrated *in vacuo* to a point where yellow solid precipitated from solution. The resulting suspension was chilled in an ice bath and filtered to give 3.84 g (55% yield) of compound **104** as a light yellow fluffy powder:

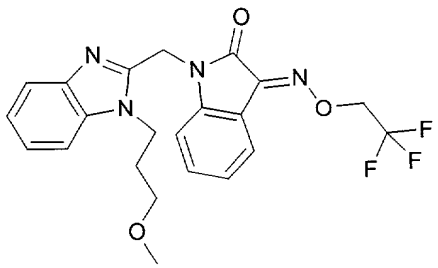
^{1}H NMR (acetone-d_6) δ 2.81 (s, 2 H), 3.30 (s, 3 H), 3.35 (t, J = 5.9 Hz, 2 H), 4.48 (t, J = 7.1 Hz, 2H), 5.33 (s, 2 H), 7.09-7.12 (m, 1 H), 7.18-7.21 (m, 1 H), 7.23-7.27 (m, 1 H), 7.33 (d, J = 7.80 Hz, 1 H), 7.37-7.41 (m, 1 H), 7.51 (d, J = 8.0 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 8.11 (d, J = 7.5 Hz, 1 H), 12.65 (s, 1 H);
MS m/e 365 (MH^+).



105

Compound **104** (219 mg, 0.60 mmol) and 2-chloro-N-(hydroxymethyl)-acetamide (148 mg, 1.2 mmol) were dissolved in anhydrous CH_3CN (50 mL). To the solution was added BEMP on polystyrene (Fluka, 1.0 g, 1.8 mmol), and the mixture was stirred at 60 °C overnight. To the resulting mixture was added PS-thiophenol resin (Argonaut, 1.0 g, 1.2 mmol), MP-carbonate resin (Argonaut, 400 mg, 1.2 mmol) and triethylamine (36 mg, 0.36 mmol) and the mixture was heated to 60 °C for 4 hours. The mixture was filtered to remove all resins and concentrated *in vacuo* to afford 136 mg (54% yield) of compound **105** as a yellow powder:

^{1}H NMR (DMSO-d_6) δ 2.00 (t, J = 6.4 Hz, 2 H), 3.25 (s, 3 H), 3.32 (t, J = 5.8 Hz, 2 H), 4.38 (t, J = 6.9 Hz, 2 H), 4.84 (s, 2 H), 5.28 (s, 2 H), 7.11-7.19 (m, 3 H), 7.22-7.25 (m, 1 H), 7.39 (s, 1 H), 7.43-7.47 (m, 1 H), 7.49 (s, 1 H), 7.53-7.57 (m, 2 H), 8.01 (d, J = 7.1 Hz, 1 H);
MS m/e 422 (MH^+).

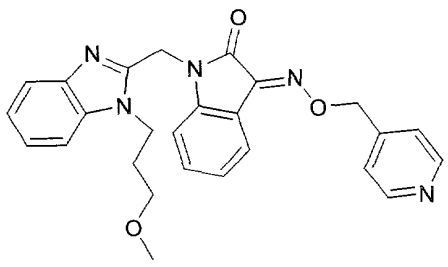


106

Compound **104** (219 mg, 0.60 mmol) and 2,2,2-trifluoroethyl-*p*-tosylate (305 mg, 1.2 mmol) were combined in anhydrous CH_3CN (50 mL). To the

solution was added BEMP on polystyrene (Fluka, 1.0 g, 1.8 mmol) and the mixture was stirred at 60 °C overnight. To the resulting mixture was added PS-thiophenol resin (Argonaut, 1.0 g, 1.2 mmol), MP-carbonate resin (Argonaut, 400 mg, 1.2 mmol) and triethylamine (36 mg, 0.36 mmol), and the mixture was heated to 60 °C for 4 hours. The mixture was filtered to remove all resins and concentrated *in vacuo*. The crude residue was dissolved in minimum CH_2Cl_2 and was diluted with diethyl ether (15 mL) and hexanes (30 mL). The resulting solution was concentrated *in vacuo* to a volume of 35 mL when solids precipitated from solution. The suspension was chilled in an ice bath, filtered and rinsed with hexanes to give 140 mg (52% yield) of compound **106** as a canary yellow powder:

^{1}H NMR (DMSO-d_6) δ 1.99 (t, J = 6.5 Hz, 2 H), 3.24 (s, 3 H), 3.31 (t, J = 5.9 Hz, 2 H), 4.37 (t, J = 7.0 Hz, 2 H), 5.19 (q, J = 9.0 Hz, 2 H), 5.28 (s, 2 H), 7.21 (m, 4 H), 7.49 (m, 1 H), 7.55 (m, 2 H), 7.92 (d, J = 7.0 Hz, 1 H);
MS m/e 447 (MH^+).

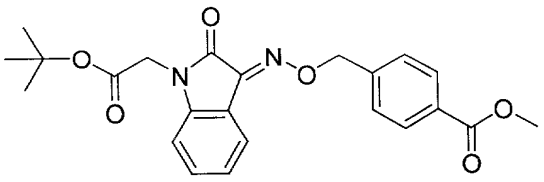


107

Compound **107** was prepared by the same procedure as described for the preparation of compound **105** with 4-(chloromethyl)pyridine hydrochloride. The crude product was purified by silica gel flash chromatography (CH_2Cl_2:CH_3OH = 40:1) to give 94 mg (34% yield) of compound **107** as a yellow solid:

^{1}H NMR (DMSO-d_6) δ 1.98 (t, J = 6.5 Hz, 2 H), 3.22 (s, 3 H), 3.28 (t, J = 5.9 Hz, 2 H), 4.36 (t, J = 7.0 Hz, 2 H), 5.27 (s, 2 H), 5.59 (s, 2 H), 7.13-7.25 (m, 4 H),

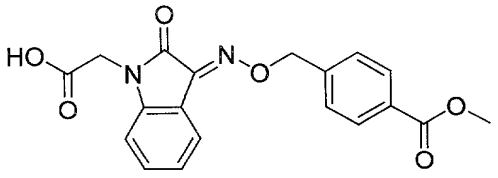
7.43-7.50 (m, 3 H), 7.54 (t, J = 8.9 Hz, 2H), 8.02 (d, J = 7.0 Hz, 1 H), 8.61-8.62 (m, 2 H);
MS m/e 456 (MH^+).



108a

A mixture of compound **95a** (3.00 g, 11.23 mmol), compound **93b** (2.14 g, 11.79 mmol), and *p*-toluenesulfonic acid (427 mg, 2.25 mmol) in MeOH (50 mL) was stirred for 1.5 hours at room temperature. The mixture was concentrated and the resulting yellow precipitate was filtered and dried to give 4.45 g (93% yield) of compound **108a**:

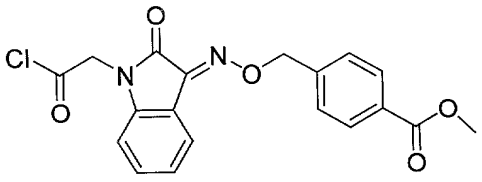
^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 3.85 (s, 3 H), 4.50 (s, 2 H), 5.59 (s, 2 H), 7.09-7.14 (m, 2 H), 7.48 (t, J = 7.8 Hz, 1 H), 7.59 (d, J = 8.2 Hz, 2 H), 7.95 (d, J = 7.4 Hz, 1 H), 7.99 (d, J = 8.2 Hz, 2 H).



108b

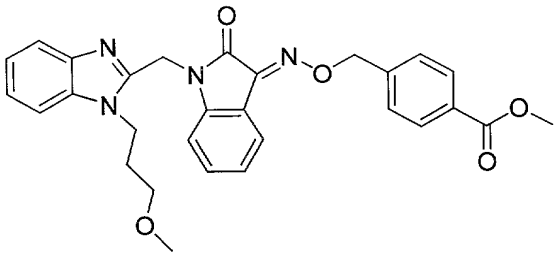
Acid **108b** was prepared using the same procedure as compound **95b** with compound **108a**:

^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3 H), 4.50 (s, 2 H), 5.60 (s, 2 H), 7.11-7.14 (m, 2 H), 7.48 (dt, J = 1.1, 7.8 Hz, 1 H), 7.59 (d, J = 8.2 Hz, 2 H), 7.95 (d, J = 6.8 Hz, 1 H), 8.00 (d, J = 8.3 Hz, 2 H).



108c

Compound **108c** was prepared using the same procedure as compound **95e** with compound **108b** and was used directly upon isolation.

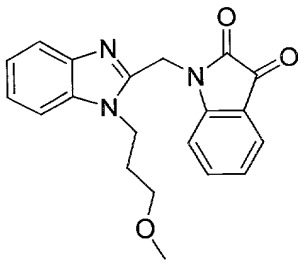


108

To a mixture of compound **103b** (233 mg, 1.29 mmol) and poly(4-vinylpyridine) (PVP, 2% cross-linked, 411 mg) in CH_2Cl_2 (15 mL) was added compound **108c** (500 mg, 1.29 mmol). The reaction mixture was stirred at room temperature for 16 hours. The PVP was removed by filtration and washed with CH_2Cl_2. The filtrate was concentrated to a minimal amount of solvent and was then diluted with Et_2O. The brown precipitate was collected by filtration. The brown solid (463 mg) was dissolved in AcOH (10 mL) and stirred at 120 °C for 1 hour. The solvent was evaporated. The residue was dissolved in the minimal amount of MeOH and diluted with Et_2O. The yellow solid was collected by filtration to give 434 mg (82% yield over two steps) of compound **108**:

^{1}H NMR (DMSO-d_6) δ 1.96-1.99 (m, 2 H), 3.22 (s, 3 H), 3.28 (t, J = 5.85, 2 H), 3.85 (s, 3 H), 4.36 (t, J = 7.0 Hz, 2 H), 5.27 (s, 3 H), 5.62 (s, 3 H), 7.12 (t, J = 7.8 Hz, 2 H), 7.17 (t, J = 7.2 Hz, 2 H), 7.25 (t, J = 7.5 Hz, 1 H), 7.45 (t, J = 7.8 Hz, 1 H), 7.54 (t, J = 9.4 Hz, 2 H), 7.61 (d, 8.2 Hz, 2 H), 7.97 (d, 7.6 Hz, 1 H), 8.01 (d, J = 8.2 Hz, 2 H);

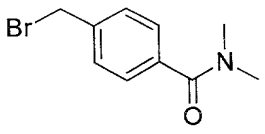
MS m/e 531 (MH^+).



109a

A solution of compound **103c** (850 mg, 2.31 mmol) in AcOH (10 mL) was stirred at 120 °C for 1 hour and then at room temperature for 18 hours. The solvent was concentrated and the brown residue was dissolved in CH_2Cl_2. To this solution was added Et_2O and the resulting brown precipitate was filtered. The solid was subjected to flash column chromatography (CH_2Cl_2/MeOH, 50:1) to give 589 mg (73% yield) of compound **109a**:

^{1}H NMR ($CDCl_3$) δ 1.94-1.99 (m, 2 H), 3.28 (t, J = 5.7 Hz, 2 H), 3.29 (s, 3 H), 4.36 (t, J = 7.2 Hz, 2 H), 5.27 (s, 2 H), 7.11 (t, J = 7.6 Hz, 1 H), 7.27-7.32 (m, 2 H), 7.39-7.41 (m, 1 H), 7.47 (d, J = 8.2 Hz, 1 H), 7.52-7.56 (m, 1 H), 7.61 (d, J = 7.6 Hz, 1 H), 7.77-7.79 (m, 1 H).

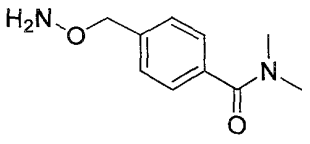


109b

To a solution of α-bromo-*p*-toluic acid (25 g, 116.25 mmol) in CH_2Cl_2 (200 mL) was added oxalyl chloride (17.71 g, 139.50 mmol) slowly followed by DMF (450 μL). The reaction was stirred approximately 1 hour until the solution became clear. The solvent was evaporated and the white solid was dried under vacuum to give the acid chloride. A mixture of the acid chloride (7.0 g, 30.24 mmol), poly(4-vinylpyridine) (PVP, 2% cross-linked, 9.6 g), and dimethylamine (2 M in THF, 15.9 mL, 31.75 mmol) in THF (200 mL) were stirred at room temperature for 15 hours. The poly(4-vinylpyridine) was removed by filtration

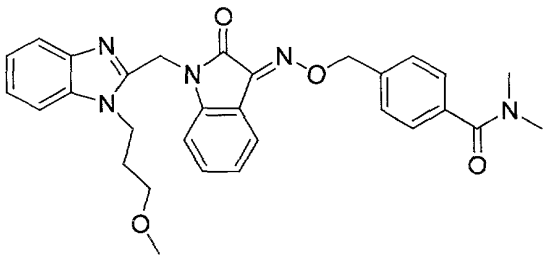
and the filtrate was concentrated to give 7.3 g (99% yield) of compound **109b** as a yellow solid:

^{1}H NMR ($CDCl_3$) δ 2.99 (s, 3 H), 3.09 (s, 3 H), 4.48 (s, 2 H), 7.38-7.43 (m, 4 H).



109c

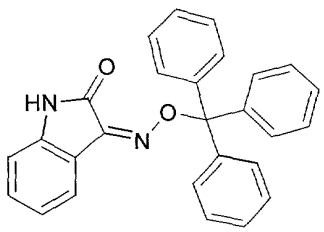
Compound **109c** was prepared using the same procedure as compound **88f** starting with compound **109b**.



109

Compound **109** was prepared using the same procedure as compound **88** with compounds **109a** and **109c**:

^{1}H NMR ($CDCl_3$) δ 2.04-2.07 (m, 2 H), 3.00 (s, 3 H), 3.13 (s, 3 H), 3.30 (s, 3 H), 3.37 (t, J = 5.3 Hz, 2 H), 4.64 (t, J = 6.7 Hz, 2 H), 5.55 (s, 2 H), 5.66 (s, 2 H), 7.10 (t, J = 7.3 Hz, 1 H), 7.39-7.50 (m, 5 H), 7.52-7.56 (m, 2 H), 7.58-7.62 (m, 2 H), 7.94 (d, J = 7.5 Hz, 1 H), 7.98 (d, J = 7.5 Hz, 1 H).

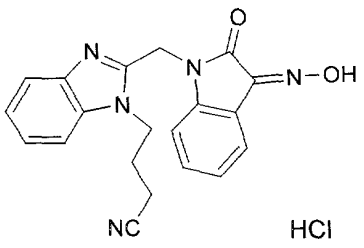


110a

Isatin (2.43 g, 16.50 mmol), *O*-tritylhydroxylamine (95%, 4.54 g, 16.5 mmol) and 1N aqueous HCl (1.7 mL, 1.70 mmol) were combined in a mixture of 100% ethanol (100 mL) and water (30 mL) and the mixture was stirred at room temperature for 1.5 hours. The reaction mixture gradually changed from a deep red color to yellow. After addition of $NaHCO_3$ (157 mg, 1.87 mmol) to neutralize the HCl, the suspension was chilled in an ice bath and filtered to isolate a yellow powder. Heating the powder at 110 °C under vacuum overnight gave 5.63 g (84% yield) of compound **110a** as a canary yellow powder:

^{1}H NMR ($CDCl_3$) δ 6.86 (d, J = 7.8 Hz, 1 H), 7.06-7.09 (m, 1H), 7.25-7.38 (m, 16 H), 7.94 (s, 1 H), 8.18 (d, J = 7.6 Hz. 1 H);

MS m/e 427 ($M+Na^+$).

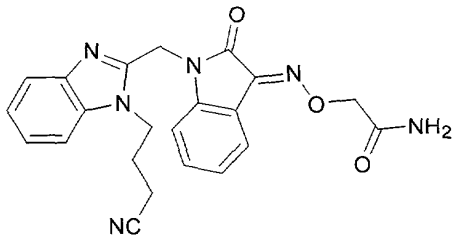


HCl **110**

A mixture of compound **110a** (3.00 g, 7.42 mmol), compound **25b** (2.00 g, 7.42 mmol) and Cs_2CO_3 (7.25g, 22.3 mmol) in anhydrous CH_3CN (70 mL) was stirred at reflux for 2 hours. The mixture was cooled to room temperature, diluted with EtOAc, and washed with water. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The crude product was dissolved in a minimum of CH_2Cl_2 and diluted with 15 volumes of MeOH while swirling. Solids precipitated from solution. The suspension was chilled in an ice bath, filtered, rinsed with ice-cold methanol, and allowed to air-dry to give the trityl oxime adduct. A solution of this intermediate (2.00 g, 3.32 mmol) in 1,4-dioxane (50 mL) was treated with 4N HCl in dioxane (8.3 mL, 33.2 mmol) and stirred at room temperature for 3 hours. The reaction mixture was filtered to isolate 1.19 g (88% yield) of compound **110** as a fluffy yellow solid:

^{1}H NMR (DMSO-d_6) δ 2.20 (t, J = 7.4 Hz, 2 H), 2.70 (t, J = 7.4 Hz, 2 H), 4.54 (t, J = 7.3 Hz, 2 H), 5.52 (s, 2 H), 7.15 (t, J = 7.5 Hz, 1 H), 7.19 (d, J = 8.0 Hz, 1 H), 7.41-7.48 (m, 3 H), 7.65 (d, J = 8.0 Hz, 1 H), 7.87 (d, J = 7.5 Hz, 1 H), 8.08 (d, J = 7.3 Hz, 1 H), 13.65 (s, 1 H);

MS m/e 360 (MH^+).

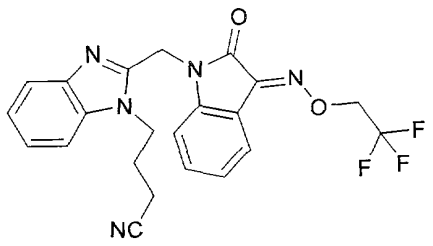


111

Compound **110** (317 mg, 0.80 mmol) and 2-chloro-N-(hydroxymethyl)-acetamide (198 mg, 1.6 mmol) were dissolved in anhydrous CH_3CN (35 mL). To the solution was added BEMP on polystyrene (Fluka, 1.2 g, 2.4 mmol), and the mixture was stirred at 60°C overnight. To the resulting mixture was added PS-thiophenol resin (Argonaut, 1.2 g, 1.6 mmol), MP-carbonate resin (Argonaut, 513 mg, 1.6 mmol) and triethylamine (36 mg, 0.36 mmol) and the mixture was heated to 60°C for 6 hours. The mixture was filtered to remove all resins and concentrated *in vacuo* to afford 201 mg (60% yield) of compound **111** as a yellow powder:

^{1}H NMR (DMSO-d_6) δ 2.13 (t, J = 7.5 Hz, 2 H), 2.64 (t, J = 7.4 Hz, 2 H), 4.40 (t, J = 7.5 Hz, 2 H), 4.84 (s, 2 H), 5.31 (s, 2 H), 7.12-7.21 (m, 3 H), 7.24-7.27 (m, 1 H), 7.38 (s, 1 H), 7.44-7.49 (m, 2 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.61 (d, J = 8.0 Hz, 1 H), 8.02 (d, J = 7.5 Hz, 1 H);

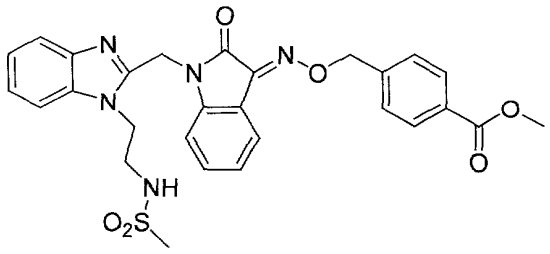
MS m/e 417 (MH^+).



112

Compound **110** (317 mg, 0.80 mmol) and 2,2,2-trifluoroethyl-*p*-tosylate (407 mg, 1.6 mmol) were dissolved in anhydrous CH_3CN (35 mL). To the solution was added BEMP on polystyrene (Fluka, 1.2 g, 2.40 mmol), and the mixture was stirred at 60 °C overnight. To the resulting mixture was added PS-thiophenol resin (Argonaut,1.2 g, 1.60 mmol), MP-carbonate resin (Argonaut, 513 mg, 1.60 mmol) and triethylamine (36 mg, 0.36 mmol), and the mixture was heated to 60 °C for 6 hours. The mixture was filtered to remove all resins and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (CH_2Cl_2:CH_3OH = 100:1) to give 224 mg (63% yield) of compound **112** as a yellow solid:

^{1}H NMR (DMSO-d_6) δ 2.13 (t, J = 7.5 Hz, 2 H), 2.64 (t, J = 7.4 Hz, 2 H), 4.40 (t, J = 7.6 Hz, 2 H), 5.19 (q, J = 9.0 Hz, 2 H), 5.31 (s, 2 H), 7.17 (t, J = 7.6 Hz, 2 H), 7.23-7.27 (m, 2 H), 7.49-7.52 (m, 1 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.61 (d, J = 8.0 Hz, 1 H), 7.92 (d, J = 7.5 Hz, 1 H);
MS m/e 442 (MH^+).



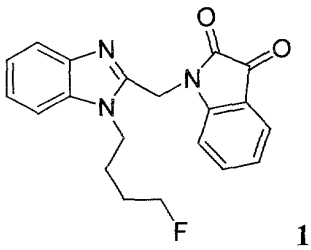
113

Compound **113** was prepared using the same procedure as compound **108** with compound **108c** and compound **23e**:

^{1}H NMR (DMSO-d_6) δ 2.81 (s, 3 H), 3.42 (t, J = 5.8 Hz, 2 H), 3.86 (s, 3 H), 4.66 (t, J = 5.4 Hz, 2 H), 5.34 (s, 2 H), 5.63 (s, 2 H), 7.12-7.19 (m, 3 H), 7.27 (t, J = 7.3 Hz, 1 H), 7.40-7.45 (m, 2 H), 7.53 (d, J = 8.0 Hz, 1 H), 7.63 (d, J = 8.3 Hz, 2 H), 7.99 (d, J = 7.3 Hz, 1 H), 8.02 (d, J = 8.3 Hz, 2 H);

NEW Spectral DATA

1-[1-(4-Fluoro-butyl)-1H-benzoimidazol-2-ylmethyl]-1H-indole-2,3-dione



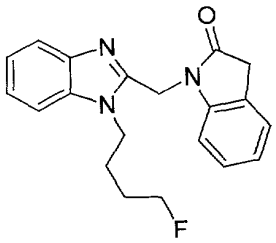
114a

1-[1-(4-Fluoro-butyl)-1H-benzoimidazol-2-ylmethyl]-1H-indole-2,3-dione was prepared as described for compound 25 starting from isatin (1.54 g, 10.5 mmol) and **159c** (2.90 g, 10.5 mmol). The product was obtained by precipitation from diethyl ether and methylene chloride to give 1-[1-(4-fluoro-butyl)-1H-benzoimidazol-2-ylmethyl]-1H-indole-2,3-dione (385 mg, 10%) as a yellow solid.

^{1}H NMR ($CDCl_3$) δ 7.79 (d, J 8.0 Hz, 1H), 7.60 (m, 3H), 7.34 (m, 3H), 7.13 (t, J 7.4 Hz, 1H), 5.28 (s, 2H), 4.46 (dt, J 5.6, 47 Hz, 2H), 4.33 (t, J 7.5 Hz, 2H), 1.82 (m, 4H);

MS m/e 352 (MH^+).

1-[1-(4-Fluoro-butyl)-1H-benzoimidazol-2-ylmethyl]-1,3-dihydro-indol-2-one

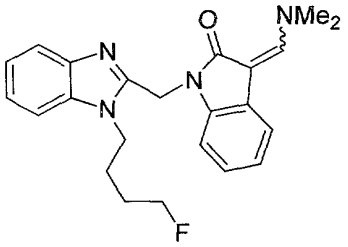


114b

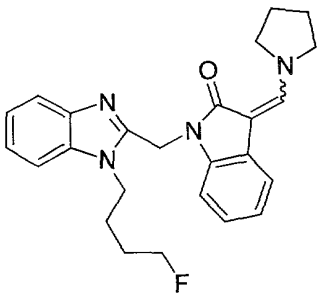
A suspension of 1-[1-(4-Fluoro-butyl)-1H-benzoimidazol-2-ylmethyl]-1H-indole-2,3-dione (607 mg, 1.73 mmol) in hydrazine hydrate (15 mL) was heated at reflux for 18 min. The solution was cooled to room temperature and quenched with ice and ethyl acetate (40 mL). The layers were separated and the aqueous phase extracted with ethyl acetate (2x40 mL). The combined organic phases were washed with brine and dried ($MgSO_4$). The product was purified by flash column chromatography (eluent 3% methanol in methylene chloride) to give compound **114b** 325 mg, 56% as an off white solid.

^{1}H NMR ($CDCl_3$) δ 7.80 (dd, J 1.9, 5.3 Hz, 1H), 7.43 (d, J 8.0 Hz, 1H), 7.29 (m, 5H), 7.02 (t, J 7.5 Hz, 1H), 5.27 (s, 2H), 4.45 (dt, J 4.9, 47 Hz, 2H), 4.32 (t, J 7.2 Hz, 2H), 3.61 (s, 2H), 1.78 (m, 4H);

MS m/e 338 (MH^+).



114



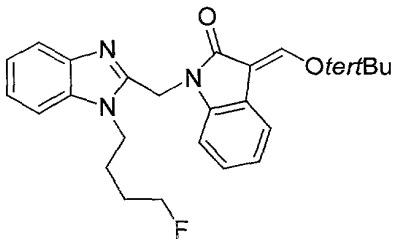
115

To a solution of the oxindole **114b** (26 mg, 0.078 mmol) in DMF (2.5 mL) was added DMF neopentyl acetal (327 μL, 1.17 mmol). The solution was stirred for 1 hour at room temperature. The volatiles were stripped off and the residue purified by flash column chromatography (eluent 3% methanol in methylene chloride). The slow moving product was the enamide **114** (10 mg, 33%) as a 2:1 mixture of geometric isomers (off white solid after trituration from diethyl ether). The fast moving product was the neopentyl enol ether, which was dissolved in methylene chloride and treated with a large excess of pyrrolidine at room temperature. After 2 hours, the volatiles were removed *in vacuo*, and the residue purified by flash column chromatography (eluent 3% methanol in

methylene chloride) to give 7 mg of the enamide **115** (3:1 mixture of geometric isomers) as an oil.

Compound **114**: ^{1}H NMR ($CDCl_3$) δ 7.80 (m, 1 H), 7.68 (s, 1H), 7.37 (d, J 7.9 Hz, 1H), 7.29 (m, 4H), 6.95 (m, 2H), 5.39 (s, 2H), 4.34 (m, 4H), 3.36 (s, 6H), 1.67 (m, 4 H);
MS m/e 393 (MH^+);

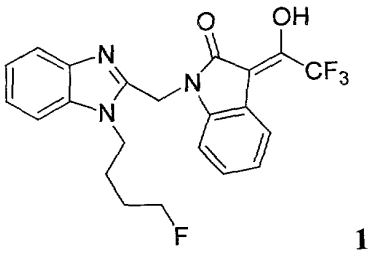
Compound **115**: ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1H), 7.79 (m, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 7.7 Hz, 1H), 7.27 (m, 3 H), 7.13 (d, J = 7.5 Hz, 1H minor isomer), 6.92 (m, 2H), 5.39, 5.38 (s, 2H), 4.30 (m, 4H), 3.83 (m, 4H), 2.04 (m, 4H), 1.66 (m, 4H);
MS m/e 419 (MH^+).



116

A solution of the oxindole **114b** (36 mg, 0.11 mmol) and DMF *tert*-Bu acetal (323 mg, 1.59 mmol) in DMF (2 mL) was stirred at 0^0C for 3 hours. The volatiles were removed *in vacuo*, and the residue purified by flash column chromatography (eluent 2%, 5% methanol in methylene chloride) to give 12 mg (fast moving product, 27%) of the enol ether **116** as a brownish oil. The slow moving product was the enamide **114** as a 2:1 mixture of geometric isomers (27 mg, 65%).

^{1}H NMR ($CDCl_3$) δ 7.93 (s, 1H), 7.79 (m, 1H), 7.61 (d, J 7.3 Hz, 1H), 7.28 (m, 4H), 7.11 (t, J = 7.4 Hz, 1H), 7.00 (t, J = 7.4 Hz, 1H), 5.31 (s, 2H), 4.35 (m, 4H), 1.68 (m, 4H), 1.53 (s, 9H);
MS m/e 422 (MH^+).

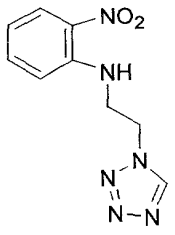


117

To a suspension of NaH (60% in mineral oil, 7.1 mg, 0.18 mmol) in THF (2 mL) was added the oxindole **114b** (40 mg, 0.12 mmol) under nitrogen. The mixture was heated at reflux temperature, and ethyl trifluoroacetate (21 μL, 0.18 mmol) was added. After 2 hours of reflux the mixture was cooled to room temperature and poured into 1M aq. HCl. The product was extracted into ethyl acetate (2x15 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$). The pure product **117** was obtained by precipitation from diethyl ether (20 mg, 38%) as a grey solid.

^{1}H NMR (DMSO) δ 7.98 (d, J = 7.5 Hz, 1H), 7.93 (d, J = 6.9 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.58 (m, 2H), 6.85 (m, 3H), 5.49 (s, 2H), 4.54 (br s, 2H), 4.35 (dt, J = 5.7, 47 Hz, 2H), 1.66 (m, 4H);

MS m/e 434 (MH^+).



118a

A mixture of amine **23c** (40 g, 220 mmol), trimethyl orthoformate (38.5 mL, 352 mmol) and sodium azide (15.7 g, 242 mmol) in acetic acid (400 mL) was heated to reflux for 12 hours. The resulting mixture was cooled to room temperature and poured into 1N HCl in ice (300 mL). The precipitate was filtered and recrystallized from EtOAc to give 19.2 g (37% yield) of compound **118a** as bright yellow needles:

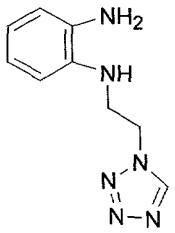
^{1}H NMR (DMSO-d_6) δ 3.90 (J = 6.6 Hz, 2 H), 4.73 (t, J = 6.6 Hz, 2 H), 6.72 (t, J = 6.9 Hz, 1H), 7.07 (d, J = 10.2 Hz, 1H), 7.53 (d, J = 6.3 Hz, 1H), 8.06 (d, J = 10.1 Hz, 1 H), 8.18 (t, J = 6.6 Hz, 1H); 9.40 (s, 1 H);

IR (KBr, cm^{-1}) 1621, 1514, 1347, 740;

MS m/e 235 (MH^+);

Anal. Calcd for $C_9H_{10}N_6O_2$: C, 46.15; H, 4.30; N, 35.88

Found: C, 46.17; H, 4.35; N, 35.85.

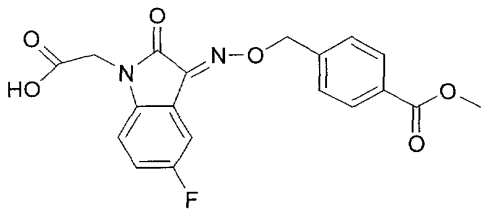


118b

A solution of compound **118a** (3.5 g, 14.95 mmol) in EtOH (50 mL) containing 10% palladium on carbon (200 mg) was hydrogenated at 50 psi for 4 hours. The reaction mixture was filtered and concentrated to give 2.8 g (93% yield) of compound **118b** as a black solid:

^{1}H NMR (DMSO-d_6) δ 3.52 (q, J = 6.0, 2 H), 4.46 (s, 3 H), 4.63-4.69 (m, 3 H), 6.45-6.57 (m, 4 H), 9.4 (s, 1 H);

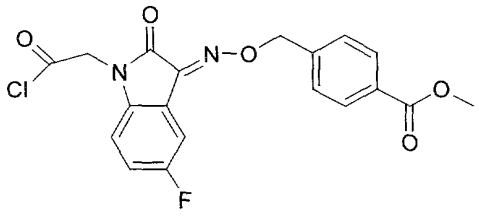
MS m/e 205 (MH^+).



118c

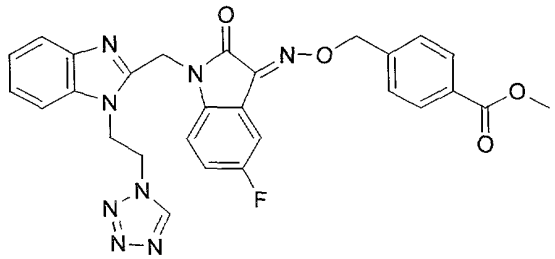
Compound **118c** was prepared using the same sequence of procedures as compound **108b** starting with 5-fluoroisatin.

^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3 H), 4.50 (s, 2 H), 5.61 (s, 2 H), 7.18 (dd, J = 4.1, 8.7 Hz, 1 H), 7.60 (d, J = 8.2 Hz, 2 H), 7.75 (dd, J = 2.7, 8.1 Hz, 1 H), 7.99 (d, J = 8.2 Hz, 2 H).



118d

Compound **118d** was prepared using the same procedure as compound **98c** with compound **118c** and was used immediately upon isolation.

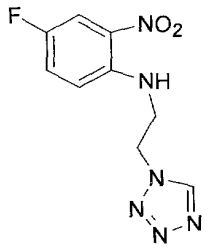


119

Compound **119** was prepared using the same procedure as compound **108** with compounds **118b** and **118d**:

^{1}H NMR (DMSO-d_6) δ 3.86 (s, 3 H), 4.88 (t, J = 5.8 Hz, 2 H), 5.02 (t, J = 5.9 Hz, 2 H), 5.12 (s, 2 H), 5.63 (s, 2 H), 7.12-7.19 (m, 2 H), 7.27-7.29 (m, 1 H), 7.35-7.39 (m, 1 H), 7.52-7.54 (m, 1 H), 7.63 (d, J = 8.3 Hz, 2 H), 7.77-7.79 (m, 1 H), 8.01 (d, J = 8.3 Hz, 2 H), 9.29 (s, 1 H);

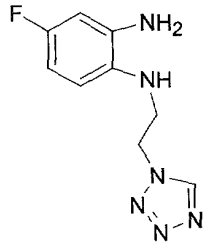
MS m/e 555 (MH^+).



120a

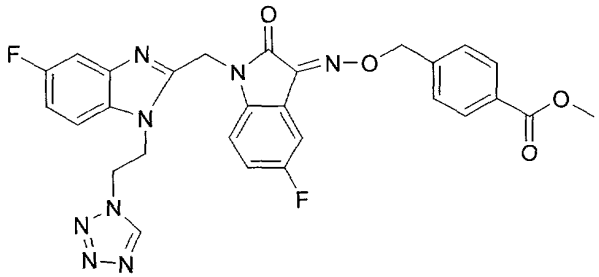
Compound **120a** was prepared using the same procedure as compound **118a** starting with 2,5-difluoronitrobenzene:

^{1}H NMR (DMSO-d_6) δ 3.88-3.92 (m, 2 H), 4.70-4.72 (m, 2 H), 7.13-7.16 (m, 1 H), 7.50-7.54 (m, 1 H), 7.86-7.89 (m, 1 H), 8.12-8.15 (m, 1 H), 9.39 (m, 1H); MS m/e 252 (MH^+).



120b

Diamine **120b** was prepared using the same procedure as compound **118b** with compound **120a** and was used directly upon isolation.

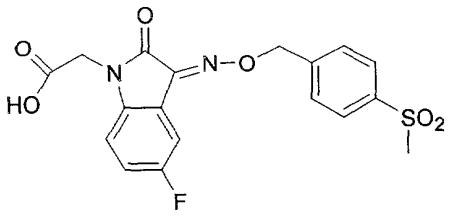


120

Compound **120** was prepared using the same procedure as compound **108** with compounds **118d** and **120b**:

^{1}H NMR (DMSO-d_6) δ 3.23 (s, 3 H), 4.85-4.89 (m, 2 H), 5.01-5.03 (m, 2 H), 5.11 (s, 2 H), 5.63 (s, 2 H), 7.01-7.07 (m, 1 H), 7.11-7.16 (m, 1 H), 7.25-7.30 (m, 1 H), 7.36-7.38 (m, 2 H), 7.63 (d, J = 8.3 Hz, 2 H), 7.80-7.82 (m, 1 H), 8.01 (d, J = 8.3 Hz, 1 H), 9.30 (s, 1 H);

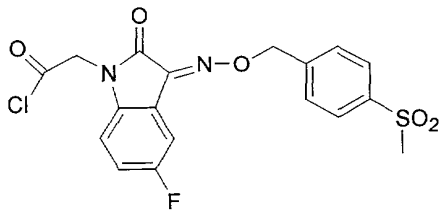
MS m/e 573 (MH^+).



121a

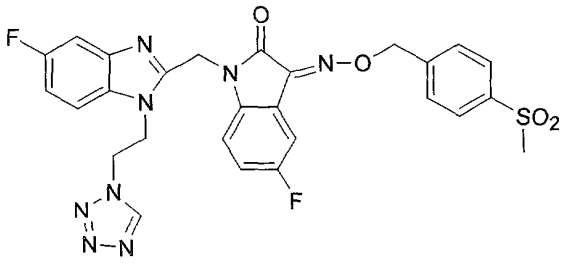
Acid **121a** was prepared using the same sequence of procedures for compound **108b** starting with 5-fluoroisatin and compound **96a**:

^{1}H NMR (DMSO-d_6) δ 3.23 (s, 3 H), 4.51 (s, 2 H), 5.65 (s, 2 H), 7.19 (dd, J = 4.1, 8.7 Hz, 1 H), 7.40 (dt, J = 2.7, 8.9 Hz, 1 H), 7.73 (d, J = 8.4 Hz, 2 H), 7.81 (dd, J = 2.7, 8.1 Hz, 1 H), 7.97 (d, J = 8.4 Hz, 2 H).



121b

Compound **121b** was prepared using the same procedure as compound **108c** with compound **121a** and was used directly upon isolation.

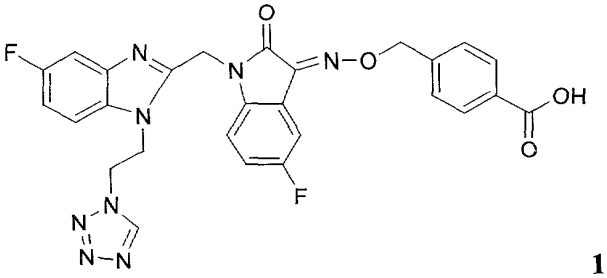


121

Compound **121** was prepared using the same procedure as compound **108** with compounds **120b** and **121b**:

^{1}H NMR (DMSO-d_6) δ 3.23 (s, 3 H), 4.85-4.89 (m, 2 H), 5.01-5.03 (m, 2 H), 5.11 (s, 2 H), 5.66 (s, 2 H), 6.96-7.01 (m, 1 H), 7.01-7.07 (m, 1 H), 7.12-7.14 (m, 1 H), 7.26-7.33 (m, 1 H), 7.38-7.41 (m, 2 H), 7.75 (d, J = 8.3 Hz, 2 H), 7.79-7.82 (m, 1 H), 7.95-7.99 (m, 3 H), 9.29 (s, 1 H);

MS m/e 593 (MH^+).

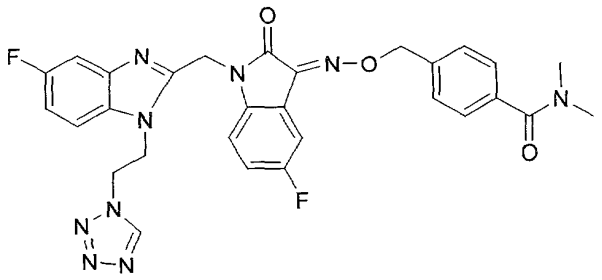


122

Compound **122** was prepared using the same procedure as compound **94** with methyl ester **120**:

^{1}H NMR (DMSO-d_6) δ 4.40 (s, 1 H), 4.79-4.81 (m, 1 H), 4.88-4.91 (m, 2 H), 5.01-5.03 (m, 1 H), 5.12 (s, 1 H), 5.36 (s, 1 H), 5.62 (s, 2 H), 6.89-6.95 (m, 1 H), 6.99-7.17 (m, 1 H), 7.29-7.32 (m, 1 H), 7.35-7.39 (m, 1 H), 7.41-7.44 (m, 1 H), 7.60 (d, J = 8.2 Hz,1 H), 7.77-7.79 (m, 1 H), 7.83 (d, J = 8.1 Hz, 1 H), 7.99 (d, J = 8.1 Hz, 2 H), 9.17 (s, 1 H), 9.30 (s, 1 H);

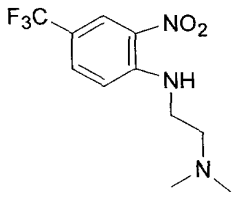
MS m/e 559 (MH^+).



123

To a solution of compound **122** (400 mg, 0.72 mmol), dimethylamine hydrochloride (87.6 mg, 1.07 mmol), and DIEA (185.1 mg, 1.43 mmol) in DMF (10 mL) was added bromotripyrrolidineophosphonium hexafluorophosphate (PyBroP®, Fluka, 400.7 mg, 0.86 mmol). The resulting mixture was stirred at room temperature for 18 hours. The mixture was diluted with MeOH (1 mL) and the solvent was evaporated. The residue was dissolved in EtOAc and washed with 5% $KHSO_4$, 5% $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and concentrated to give 300 mg (72% yield) of compound **123** as a yellow solid:

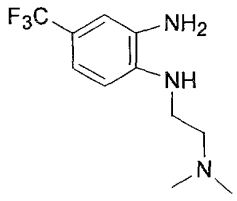
^{1}H NMR (DMSO-d_6) δ 2.91 (s, 3 H), 2.98 (s, 3 H), 4.88-4.90 (m, 2 H), 5.01-5.03 (m, 2 H), 5.11 (s, 2 H), 5.58 (s, 2 H), 7.02-7.07 (m, 1 H), 7.14-7.17 (m, 1 H), 7.27-7.32 (m, 1 H), 7.33-7.39 (m, 2 H), 7.45 (d, J = 8.2 Hz, 2 H), 7.54 (d, J = 8.1 Hz, 2 H), 7.76-7.78 (m, 1 H), 9.30 (s, 1 H);
MS m/e 586 (MH^+).



124a

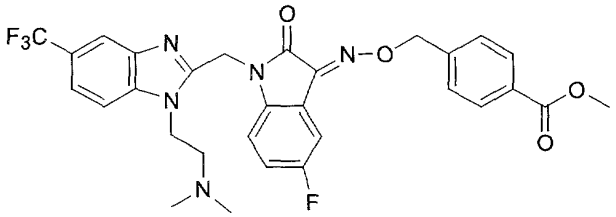
Compound **124a** was prepared using the same procedure as compound **98a** with 4-fluoro-3-nitrobenzotrifluoride:

^{1}H NMR (DMSO-d_6) δ 2.22 (s, 6 H), 2.55 (t, J = 6.2 Hz, 2 H), 3.43-3.47 (m, 2 H), 7.22 (d, J = 8.8 Hz, 1 H), 7.81 (dd, J = 2.2, 9.2 Hz, 1 H), 8.32 (s, 1 H), 8.60 (t, J = 4.5 Hz, 1 H);
MS m/e 278 (MH^+).



124b

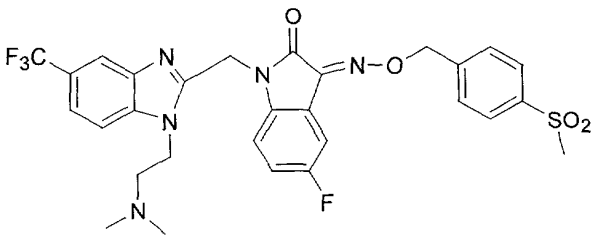
Compound **124b** was prepared using the same procedure as compound **98b** with compound **124a** and was used directly upon isolation.



124

Compound **124** was prepared using the same procedure as compound **108** with compound **118d** and **124b**:

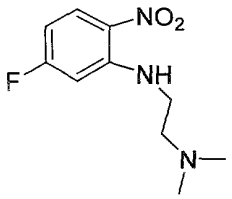
^{1}H NMR (DMSO-d_6) δ 2.50 (s, 6 H), 3.86 (s, 3 H), 4.75-4.85 (bs, 2 H), 5.41 (s, 2 H), 5.64 (s, 2 H), 5.58 (s, 2 H), 7.17-7.26 (m, 1 H), 7.37-7.39 (m,1 H), 7.63 (d, J = 8.0 Hz, 3 H), 7.80-7.82 (m, 1 H), 7.88-7.96 (m, 1 H), 7.99-8.03 (m, 3 H);
MS m/e 598 (MH^+).



125

Compound **125** was prepared using the same procedure as compound **108** with compound **121b** and **124b**:

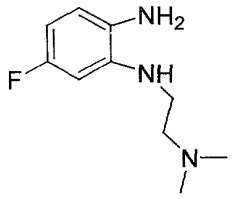
^{1}H NMR (DMSO-d_6) δ 2.90 (d, J = 4.8 Hz, 6 H), 3.24 (s, 3 H), 4.84-4.86 (m, 4 H), 5.44 (s, 2 H), 5.67 (s, 2 H), 7.24-7.27 (m, 1 H), 7.36-7.42 (m, 1 H), 7.63-7.64 (m, 1 H), 7.76 (d, J = 8.3 Hz, 2 H), 7.84-7.87 (m, 1 H), 7.98-8.00 (m, 4 H);
MS m/e 618 (MH^+).



126a

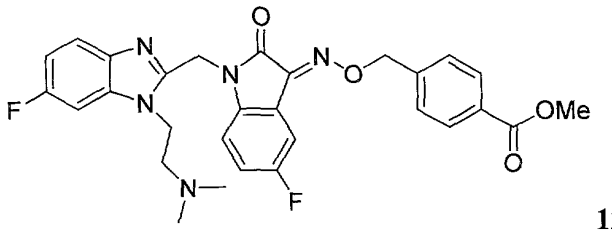
Compound **126a** was prepared using the same procedure as compound **98a** with 2,4-difluoronitrobenzene:

^{1}H NMR ($CDCl_3$) δ 2.21 (s, 6 H), 2.53 (t, J = 6.1 Hz, 2 H), 3.33-3.37 (m, 2 H), 6.51-6.56 (m, 1 H), 6.85 (dd, J = 2.7, 12.2 Hz, 1 H), 8.17 (dd, J = 6.3, 9.5 Hz, 1 H), 8.42 (bs, 1 H);
MS m/e 228 (MH^+).



126b

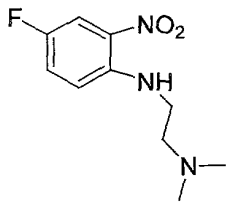
Compound **126b** was prepared using the same procedure as compound **98b** with compound **126a** and was used immediately upon isolation.



126

Compound **126** was prepared using the same procedure as compound **108** with compound **118d** and **126b**:

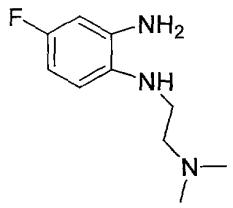
^{1}H NMR ($CDCl_3$) δ 2.94 (s, 6 H), 3.32 (bs, 2 H), 3.94 (s, 3 H), 4.97 (bs, 2 H), 5.28 (s, 2 H), 5.61 (s 2 H), 7.05 (t, J = 13.6 Hz, 1 H), 7.16 (dt, J = 4.3, 14.5 Hz, 1 H), 7.51 (d, J = 13.5 Hz, 3 H), 7.69-7.63 (m, 3 H), 8.08 (d, J = 13.7 Hz, 2 H).



127a

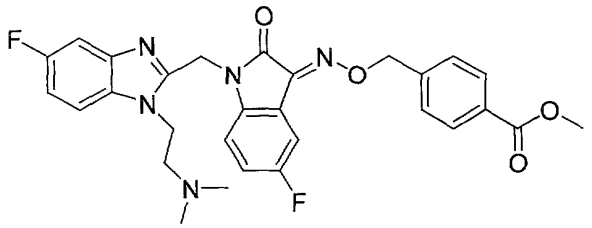
Compound **127a** was prepared using the same procedure as compound **98a** with 2, 5-difluoronitrobenzene:

^{1}H NMR (DMSO-d_6) δ 2.21 (s, 6 H), 2.53 (t, J = 6.05 Hz, 2 H), 3.35-3.39 (m, 2 H), 7.08 (dd, J = 4.8, 9.52 Hz, 1 H), 7.50-7.55 (m, 1 H), 7.83 (dd, J = 3.0, 9.5 Hz, 1 H), 8.22 (bs, 1 H);
MS m/e 227 (MH^+).



127b

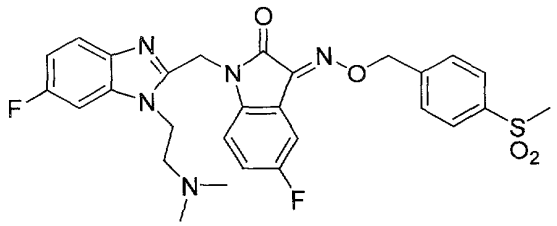
Compound **127b** was prepared using the same procedure as compound **98b** with compound **127a** and was used immediately upon isolation.



128

Compound **128** was prepared using the same procedure as compound **108** with compound **118d** and **127b**:

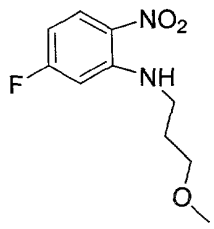
^{1}H NMR ($CDCl_3$) δ 2.94 (s, 6 H), 3.27-3.44 (m, 2 H), 3.93 (s, 3 H), 5.01 (m, 2 H), 5.29 (s, 2 H), 5.69 (s, 2 H), 7.15 (d, J = 9.6 Hz, 2 H), 7.41 (d, J = 12.4 Hz, 1 H), 7.50 (d, J = 12.6 Hz, 3 H), 7.67 (d, J = 9.5 Hz, 1 H), 7.88 (bs, 1 H), 8.07 (d, J = 12.1 Hz, 2 H).



129

Compound **129** was prepared using the same procedure as compound **108** with compound **121b** and **126b**:

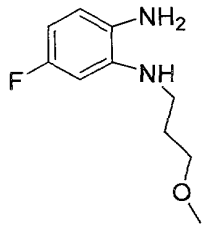
^{1}H NMR (DMSO-d_6) δ 2.85 (s, 6 H), 3.23 (s, 3 H) 3.52 (bs, 2 H), 4.76 (t, J = 7.5, 2 H), 5.36 (s, 2 H), 5.67 (s, 2 H), 7.05 (dt, J = 2.2, 9.0 Hz, 1 H), 7.26 (dd, J = 4.1, 8.7 Hz, 1 H), 7.39 (dt, J = 2.6, 9.1 Hz, 1 H), 7.57 (dd, J = 4.9, 8.7 Hz, 1 H), 7.71 (d, J = 9.4 Hz, 1 H), 7.75 (d, J = 8.2 Hz, 2 H), 7.84 (dd, J = 2.6, 8.0 Hz, 1 H), 7.98 (d, J = 8.2 Hz, 2 H).



130a

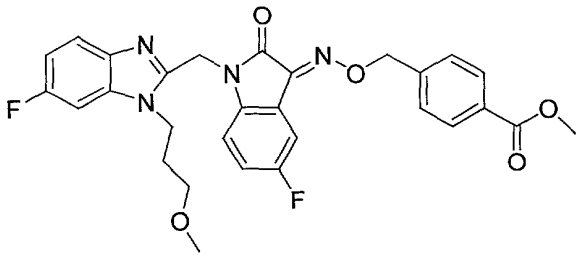
Compound **130a** was prepared using the same procedure as compound **103a** starting with 2,4-difluoronitrobenzene:

^{1}H NMR ($CDCl_3$) δ 1.89-2.04 (m, 2 H), 3.29, 3.28-3.44 (s over m, 5 H), 3.54 (t, J = 5.7 Hz, 2 H), 6.33-6.37 (m, 1 H), 6.52 (dd, J = 2.7, 11.5 Hz, 1 H), 8.22 (dd, J = 6.3, 9.5 Hz, 1 H), 8.44 (bs, 1 H).



130b

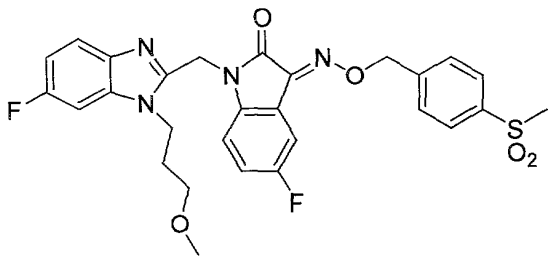
Compound **130b** was prepared using the same procedure as compound **103b** with compound **130a** and was used immediately upon isolation.



130

Compound **130** was prepared using the same procedure as compound **108** with compounds **118d** and **130b**:

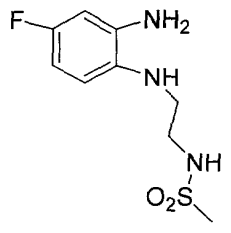
^{1}H NMR ($CDCl_3$) δ 1.96-1.99 (m, 2 H), 2.12 (s, 3 H), 3.32 (s, 3 H), 3.32 (t, J = 9.0 Hz, 2 H), 3.94 (s, 3 H), 4.38 (t, J = 11.6 Hz, 2 H), 5.29 (s, 2 H), 5.61 (s, 2 H), 7.05-7.13 (m, 3 H), 7.42 (dd, J = 6.6, 14.3 Hz, 1H), 7.52 (d, J = 13.5 Hz, 2 H), 7.65-7.73 (m, 2 H), 8.08 (d, J = 13.6 Hz, 2 H).



131

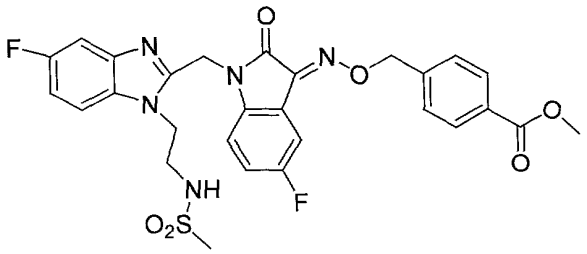
Compound **131** was prepared using the same procedure as compound **98** with compounds **121b** and **130b**:

^{1}H NMR (DMSO-d_6) δ 1.96-1.98 (m, 2 H), 3.21 (s, 3 H), 3.23 (s, 3 H), 3.35 (bs, 2 H), 4.33 (t, J = 6.2 Hz, 2 H), 5.25 (s, 2 H), 5.66 (s, 2 H), 7.01 (t, J = 8.9 Hz, 1 H), 7.20 (t, J = 4.2 Hz, 1 H), 7.37 (t, J = 7.7 Hz, 1 H), 7.45 (d, J = 8.4 Hz, 1 H), 7.55 (dd, J = 4.5, 8.4 Hz, 1 H), 7.75 (d, J = 7.7 Hz, 2 H), 7.83 (d, J = 6.9 Hz, 1 H), 7.98 (d, J = 7.9 Hz, 2 H).



132a

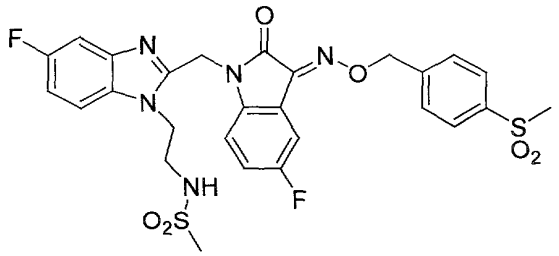
Compound **132a** was prepared using the same procedure as compound **23e** starting with 2,5-difluoronitrobenzene and was used immediately upon isolation.



132

Compound **132** was prepared using the same procedure as compound **108** with compounds **118d** and **132a**:

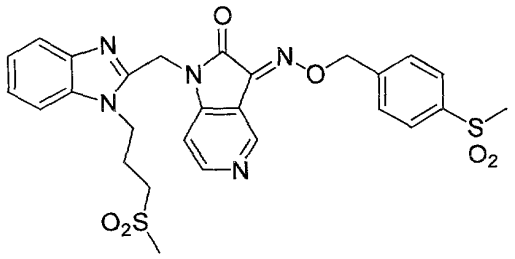
^{1}H NMR (DMSO-d_6) δ 2.83 (s, 3 H), 3.41 (q, J = 5.9 Hz, 2 H), 3.86 (s, 3 H), 4.46 (t, J = 5.8 Hz, 2 H), 5.33 (s, 2 H), 5.64 (s, 2 H), 7.13-7.19 (m, 2 H), 7.33 (dt, J = 2.7, 9.1 Hz, 1 H), 7.34-7.44 (m, 2 H), 7.64 (d, J = 8.2 Hz, 3 H), 7.80 (dd, J = 2.7, 8.1 Hz, 1 H), 8.02 (d, J = 8.3 Hz, 2 H).



133

Compound **133** was prepared using the same procedure as compound **108** with compounds **121b** and **132a**:

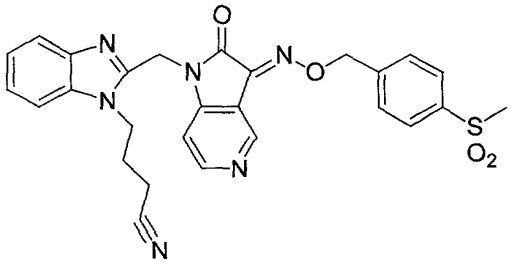
^{1}H NMR (DMSO-d_6) δ 2.86 (s, 3 H), 3.24 (s, 3 H), 3.39-3.43 (m, 2 H), 4.48 (t, J = 5.7 Hz, 2 H), 5.36 (s, 2 H), 5.67 (s, 2 H), 7.17-7.20 (m, 2 H), 7.34 (dt, J = 2.5, 9.1 Hz, 1 H), 7.45-7.39 (m, 2 H), 7.68 (dd, J = 4.8, 9.0 Hz, 1 H), 7.76 (d, J = 8.4 Hz, 2 H), 7.85 (dd, J = 2.7, 8.1 Hz, 1 H), 7.99 (d, J = 8.4 Hz, 2 H).



133a

To a solution of 1H-pyrrolo[3,2-c]pyridine-2,3-dione (0.45 g, 3.1 mmol) [prepared as described in Rivalle, *J. Het. Chem.*, **1997**, *34*, 491.] in MeOH (20 ml) was added p-toluenesulfonic acid (0.6 g, 3.1 mmol) and O-(4-methanesulfonyl-benzyl)-hydroxylamine (0.62 g, 3.1 mmol). The mixture was stirred areflux for 12h then cooled and filtered. The solid was the desired 1H-pyrrolo[3,2-c]pyridine-2,3-dione 3-[O-(4-methanesulfonyl-benzyl)-oxime which was used without further purification as described for the preparation of **134** using **10d** and the compound above with BTPP as base to give **133a**.

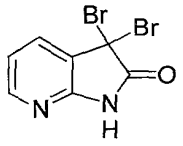
^{1}HNMR (DMSO) δ: 2.20-2.23 (m, 2 H), 3.00 (s, 3 H), 3.25-3.30 (m, 2 H), 4.45-4.48 (m, 2 H), 5.33 (s, 2 H), 5.70 (s, 2 H), 7.17 (t, J = 7.5 Hz, 1 H), 7.26 (t, J = 7.7 Hz, 1 H), 7.32 (d, J = 5.25 Hz, 1 H), 7.54 (d, J = 8.0 Hz, 1 H), 7.63 (d, J = 8.1 Hz, 1 H), 7.76 (d, J = 8.3 Hz, 2 H), 7.98 (d, 8.3 Hz, 2 H), 8.56 (d, J = 5.4 Hz, 1 H), 9.02 (s, 1 H);
MS m/e 581 (MH^+).



133b

Compound **133b** was prepared as described for **133a** using compound **25b** and BTPP as base.

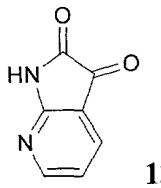
^{1}HNMR (DMSO) δ: 2.10-2.17 (m, 2 H), 2.60-2.65 (m, 2 H), 3.23 (s, 3 H), 4.35-4.42 (m, 2 H), 5.32 (s, 2 H), 5.70 (s, 2 H), 7.16 (t, J = 7.3 Hz, 1 H), 7.29 (t, J = 7.3 Hz, 1 H), 7.31 (d, J = 6.5 Hz, 1 H), 7.55 (d, J = 8.1 Hz, 1 H), 7.62 (d, J = 8.1 Hz, 1 H), 7.77 (d, J = 8.3 Hz, 2 H), 7.98 (d, J = 8.3 Hz, 2 H), 8.56 (d, J = 6.5 Hz, 1 H), 9.03 (s, 1 H);
MS m/e 528 (MH^+).



134a

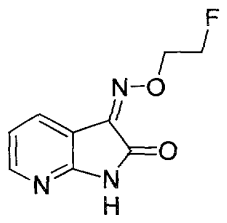
3,3-Dibromo 7-aza oxindole **134a** was prepared using a procedure described by Marfat, etc (*Tetrahedron Lett.*, **1987**, *28*, 4027-4031) or using the procedure below.

To a solution of 7-azaindole (2.0 g, 0.016 mol) in *tert.* BuOH (120 mL) was added $PyBr_3$ in portions. The resulting mixture was stirred at room temperature for 15 hours. The solvent was removed *in vacuo* and the residue was suspended in water (250 mL). The aqueous phase was extracted with ethyl acetate (2 x 150 mL) and the combined organic fractions were washed with water (2 x 100 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and evaporated. The residue was triturated in methylene chloride and filtered to afford 3.72 g of compound **134a** (80%) as a white-brown solid:
^{1}H NMR ($CDCl_3$) δ 8.25 (dd, J = 1.4, 5.3 Hz, 1H), 7.88 (dd, J = 1.4, 7.6 Hz, 1H), 7.16 (dd, J = 5.3, 7.6 Hz, 1H);
MS m/e 293 (MH^+).



134b

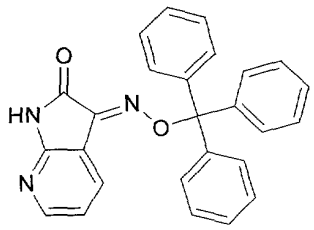
Compound **134b** was prepared from the dibromide above according to the procedure described by J. Lloyd et al. (*Bioorganic and Medicinal Chemistry Letters*, **1994**, *4*, 195-200).



134c

A solution of compound **134b** (300 mg, 1.03 mmol) in DMSO (25 mL) was heated at 95^{0}C under house vacuum for 6.5 hours. The solution containing the corresponding 7-aza isatin was cooled to room temperature, followed by the addition O-(2-Fluoro-ethyl)-hydroxylamine hydrochloride(prepared as described by Ishikawa et al *J. Antibiot.*, **2000**, *53*, 1071) (131 mg, 1.13 mmol). After stirring for 1 hour at room temperature the mixture was quenched with water and extracted with ethyl acetate (6 x 25 mL). The combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (gradient, 2% MeOH in methylene chloride to 3%) to give compound **134c** (200 mg, 93%) as an orange solid that was further purified by trituration from diethyl ether-methylene chloride (1:1).

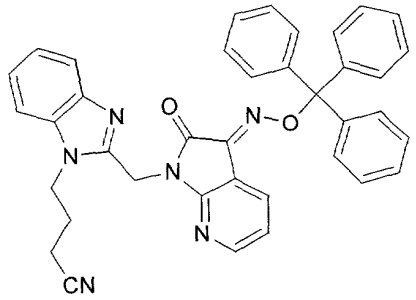
^{1}H NMR (DMSO) δ 11.5 (s, 1 H), 4.57-4.84 (m, 4 H), 7.08 (m, 1 H), 8.10 (d, J = 7.0 Hz, 1 H), 8.24 (d, J = 4.1 Hz, 1 H);
MS m/e 210 (MH^+).



134d

Compound **134b** (0.972 g, 6.56 mmol) was combined with *o*-tritylhydroxylamine (1.90 g, 6.56 mmol) in a mixture of EtOH (20 mL) and water (5 mL). The resulting mixture was briefly heated to boiling with a heat gun and then allowed to cool to room temperature. The suspension was chilled in an ice bath and filtered to isolate the crude pink solid which was rinsed with a mixture of cold 4:1 ethanol:water. The solid was dissolved with heating in chloroform and the resulting warm solution was passed through a plug of silica gel to remove the pink contaminant. Concentration *in vacuo* afforded 1.67 g (63% yield) of compound **134d** as a yellow powder:

^{1}H NMR (DMSO-d_6) δ 7.15 (dd, J = 7.4 Hz, 5.3 Hz, 1 H), 7.27-7.28 (m, 6 H), 7.34-7.42 (m, 9 H), 8.24 (dd, J = 7.5 Hz, 1.4 Hz, 1 H), 8.27 (dd, J = 5.3 Hz, 1.5 Hz), 11.47 (s, 1 H);
MS m/e 428 ($M+Na^+$), 833 ($2M+Na^+$).

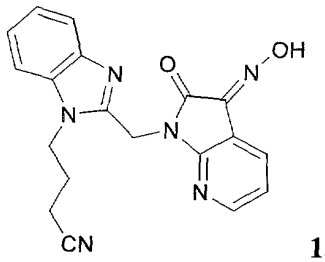


134

Compound **134d** (0.75 g, 1.85 mmol) was combined with cesium carbonate (1.81 g, 5.55 mmol) in DMF (20 mL), and the suspension was stirred at room temperature for 10 minutes. Compound **25b** (0.50 g, 1.85 mmol) was

added. The orange mixture was stirred at room temperature for 4.3 hours and the color of the reaction mixture became olive green all at once. The reaction mixture was diluted with ethyl acetate (100 mL) and water (100 mL). The phases were separated, and the organic layer was washed with water (2 x 50 mL) and brine (50 mL). The deep olive green mixture was dried over anhydrous $MgSO_4$ and it slowly became orange in color. The mixture was filtered and the filtrate concentrated *in vacuo*. The resulting crude solid was recrystallized from EtOAc to give 0.98 g (88% yield) of compound **134** as a yellow powder:

^{1}H NMR (DMSO-d_6) δ 2.13-2.16 (m, 2 H), 2.63 (t, J = 7.4 Hz, 2 H), 4.42 (t, J = 7.4 Hz, 2 H), 5.24 (s, 2 H), 7.13-7.16 (m, 1 H), 7.22-7.26 (m, 2 H), 7.31-7.32 (m, 6 H), 7.36-7.39 (m, 3 H), 7.41-7.44 (m, 6 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.59 (d, J = 8.1 Hz, 1 H), 8.28 (dd, J = 1.6, 5.4 Hz, 1 H), 8.34 (dd, J = 1.6, 7.5 Hz, 1 H); MS m/e 603 (MH^+).

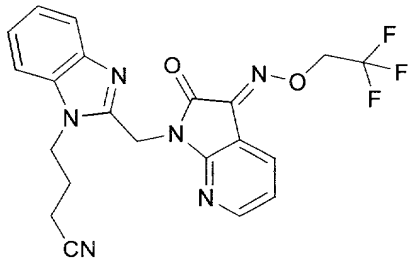


135

Compound **134** (0.50 g, 0.83 mmol) and *p*-toluenesulfonic acid monohydrate (0.141 g, 0.75 mmol) were combined in anhydrous CH_3CN (8 mL) in a sealed tube and the mixture was heated to 100 °C for 1 hour. Upon cooling, the product came out of solution as spherical crystals. The crystals were filtered from the mixture and rinsed with cold CH_3CN to give 0.39 g (86% yield) of compound **135** as a mono-*p*-toluenesulfonic acid salt:

^{1}H NMR (DMSO-d_6) δ 2.26 (t, J = 7.6 Hz, 2 H), 2.29 (s, 3 H), 2.72 (t, J = 7.5 Hz, 2 H), 4.67 (t, J = 7.4 Hz, 2 H), 5.60 (s, 2 H), 7.11 (d, J = 8.1 Hz, 2 H), 7.19 (dd, J = 5.4, 7.4 Hz, 1 H), 7.47 (d, J = 8.3 Hz, 2 H), 7.56 (t, J = 7.7 Hz, 1 H), 7.62 (t, J =

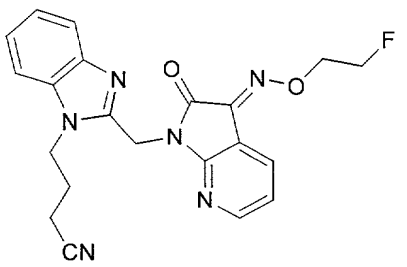
7.7 Hz, 1 H), 7.73 (d, J = 8.0 Hz, 1 H), 8.04 (d, J = 8.3 Hz, 1 H), 8.22 (dd, J = 1.6, 5.3 Hz, 1 H), 8.30 (dd, J = 1.6, 7.5 Hz, 1 H), 13.99 (s, 1 H);
MS m/e 361 (MH^+).



136

Compound **135** (68 mg, 0.12 mmol), 2,2,2-trifluoroethyl *p*-toluenesulfonate (0.035 g, 0.135 mmol) and BEMP on polystyrene (Fluka, 0.17 g, 0.37 mmol) were combined in anhydrous CH_3CN (3 mL) and the mixture was heated to 70 °C for 48 hours. Solids were removed from the mixture by filtration and rinsed with methanol. The filtrate was concentrated *in vacuo*, and the crude product was purified by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 25 mg (36% yield) of a trifluoroacetic acid salt of compound **136** as a yellow glassy solid:

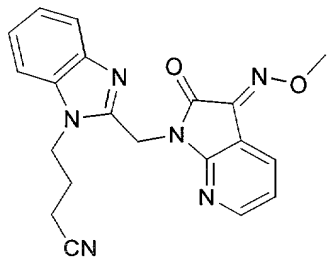
^1H NMR (DMSO-d_6) δ 2.18-2.24 (m, 2 H), 2.68 (t, J = 7.4 Hz, 2 H), 4.53 (t, J = 7.4 Hz, 2 H), 5.24 (q, J = 8.9 Hz, 2 H), 5.42 (s, 2 H), 7.23 (dd, J = 5.4, 7.5 Hz, 1 H), 7.33 (t, J = 7.5 Hz, 1 H), 7.41 (t, J = 7.4 Hz, 1 H), 7.62 (d, J = 8.0 Hz, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 8.19 (dd, J = 1.5, 7.5 Hz, 1 H), 8.30 (dd, J = 1.5, 5.3 Hz, 1 H);
MS m/e 443 (MH^+).



137

Compound **137** was prepared using the same procedure as compound **136**. Excess electrophile was scavenged by the addition of PS-thiophenol resin (Argonaut, 100 mg), which was stirred with the reaction mixture for 4 hours. Purification by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) gave 15 mg (23 % yield) of a trifluoroacetic acid salt of compound **137** as a red glassy solid:

^{1}H NMR (DMSO-d_6) δ 2.18-2.24 (m, 2 H), 2.68 (t, J = 7.4 Hz, 2 H), 4.53 (t, J = 7.4 Hz, 2 H), 4.78-4.80 (m, 2 H), 4.81 (dt, J = 3.7, 81.8 Hz, 2 H), 5.42 (s, 2 H), 7.20 (dd, J = 5.3, 7.4 Hz, 1 H), 7.34 (t, J = 7.6 Hz, 1 H), 7.41 (t, J = 7.6 Hz, 1 H), 7.60 (d, J = 8.1 Hz, 1 H), 7.78 (d, J = 7.7 Hz, 1 H), 8.24-8.27 (m, 2 H); MS m/e 407 (MH^+).

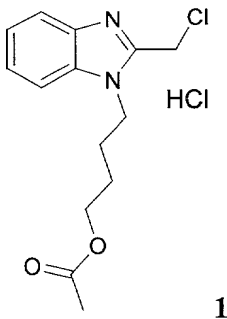


138

A mixture of compound **135** (68 mg, 0.12 mmol), cesium carbonate (0.12 g, 0.37 mmol) and iodomethane (19 mg, 0.14 mmol) in anhydrous CH_3CN (3 mL) was stirred for 18 hours at room temperature. The mixture became a deep olive green color during the course of the reaction. Excess iodomethane was scavenged by the addition of PS-thiophenol resin (Argonaut, 100 mg), which was stirred with the reaction mixture for 2 hours. Solids were removed by filtration and rinsed with MeOH. The filtrate was concentrated *in vacuo* to a green solid. The crude product was purified by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 12 mg (20% yield) of a trifluoroacetic acid salt of compound **138** as a red glassy solid:

^{1}H NMR (DMSO-d_6) δ 2.17-2.23 (m, 2 H), 2.68 (t, J = 7.4 Hz, 2 H), 4.29 (s, 3 H), 4.53 (t, J = 7.4 Hz, 2 H), 5.42 (s, 2 H), 7.17 (dd, J = 5.3, 7.4 Hz, 1 H), 7.32 (t, J = 7.5 Hz, 1 H), 7.40 (t, J = 7.5 Hz, 1 H), 7.60 (d, J = 8.0 Hz, 1 H), 7.78 (d, J = 8.0 Hz, 1 H), 8.21 (dd, J = 1.5, 7.4 Hz, 1 H), 8.25 (dd, J = 1.5, 5.3 Hz, 1 H);

MS m/e 375 (MH^+).

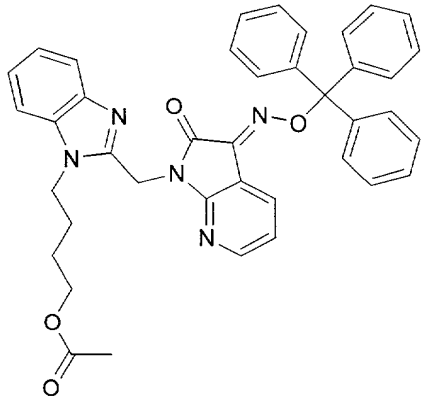


139a

Compound **139a** was prepared using the same procedure as compound **25b** with 4-bromobutyl acetate:

^{1}H NMR ($CDCl_3$) δ 1.80-1.86 (m, 2 H), 2.03 (s, 3 H), 2.06-2.12 (m, 2 H), 4.14 (t, J = 6.1 Hz, 2 H), 4.55 (t, J = 8.1 Hz, 2 H), 5.42 (s, 2 H), 7.48 (t, J = 7.3 Hz, 1 H), 7.55 (t, J = 7.3 Hz, 1 H), 7.64 (d, J = 8.5 Hz, 1 H), 7.78 (d, J = 8.2 Hz, 1 H);

MS m/e 281 (MH^+).

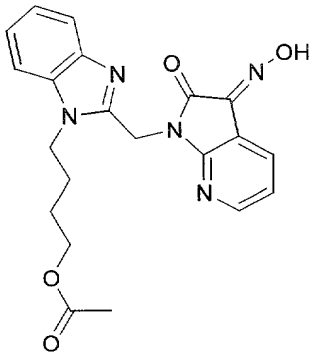


139

A mixture of compound **134b** (0.75 g, 1.85 mmol) and cesium carbonate (1.81 g, 5.55 mmol) in DMF (20 mL) was stirred at room temperature for 10

minutes. After addition of compound **139a** (0.59 g, 1.85 mmol), the orange mixture was stirred at room temperature for 2.5 hours and the reaction mixture became olive green in color. The reaction mixture was diluted with EtOAc (100 mL) and water (100 mL). The phases were separated and the organic layer was washed with water (2 x 50 mL) and brine (50 mL). The deep olive green organic layer was dried over anhydrous $MgSO_4$ and it slowly became orange in color. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography (CH_2Cl_2:CH_3OH, 50:1) and then recrystallized from EtOAc to give 0.73 g (61% yield) of compound **139** as a yellow powder:

^{1}H NMR (DMSO-d_6) δ 1.63-1.67 (m, 2 H), 1.82-1.85 (m, 2 H), 4.03 (t, J = 6.5 Hz, 2 H), 4.38 (t, J = 7.3 Hz, 2 H), 5.22 (s, 2 H), 7.11-7.14 (m, 1 H), 7.20-7.26 (m, 2 H), 7.31-7.32 (m, 6 H), 7.36-7.39 (m, 3 H), 7.41-7.44 (m, 6 H), 7.49 (d, J = 8.0 Hz, 1 H), 7.58 (d, J = 8.1 Hz, 1 H), 8.28 (dd, J = 1.6, 5.4 Hz, 1 H), 8.35 (dd, J = 1.6, 7.5 Hz, 1 H);
MS m/e 650 (MH^+).

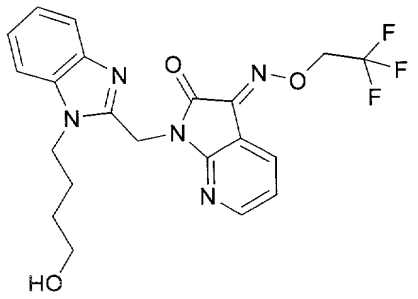


140

Compound **140** was prepared using the same procedure as compound **135**. Purification by flash chromatography (gradient, CH_2Cl_2:CH_3OH, 30:1 to 10:1) gave 0.15 g (70% yield) of compound **140** as a yellow glassy solid:

^{1}H NMR (DMSO-d_6) δ 1.66-1.69 (m, 2 H), 1.84-1.87 (m, 2 H), 1.99 (s, 3 H), 4.05 (t, J = 6.5 Hz, 2 H), 4.40 (t, J = 7.4 Hz, 2 H), 5.27 (s, 2 H), 7.12-7.15 (m, 2 H),

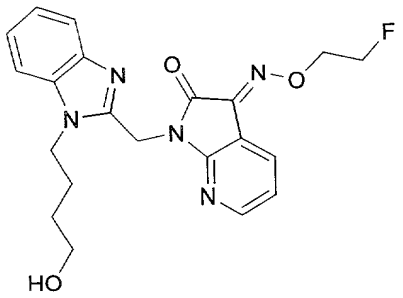
7.22 (t, J = 8.1 Hz, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 7.59 (d, J = 8.1 Hz, 1 H), 8.21 (dd, J = 1.6, 5.3 Hz, 1 H), 8.27 (dd, J = 1.6, 7.4 Hz, 1 H), 13.89 (s, 1 H);
MS m/e 408 (MH^+).



141

A mixture of compound **140** (0.05 g, 0.12 mmol), 2,2,2-trifluoroethyl *p*-toluenesulfonate (0.035 g, 0.14 mmol) and BEMP on polystyrene (Fluka, 0.17 g, 0.37 mmol) in anhydrous CH_3CN (3 mL) was heated to 70 °C for 18 hours. MeOH (1 mL) was added to remove the acetate group and the mixture was heated to 70 °C for 4 hours. Solids were removed by filtration and rinsed with methanol. The filtrate was concentrated *in vacuo*, and the crude product was purified by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 0.025 g (37% yield) of a trifluoroacetic acid salt of compound **141** as an off-white powder:

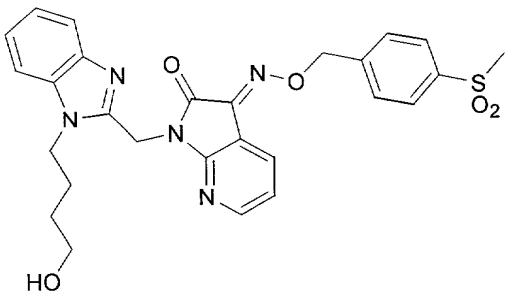
^1H NMR (DMSO-d_6) δ 1.50-156 (m, 2 H), 1.85-1.91 (m, 2 H), 3.42-3.49(m, 2 H), 4.50 (t, J = 7.4 Hz, 2 H), 5.24 (q, J = 9.0 Hz, 2 H), 5.43 (s, 2 H), 7.23-7.27 (m, 1 H), 7.36-7.38 (m, 1 H), 7.42-7.45 (m, 1 H), 7.63 (d, J = 8.1 Hz, 1 H), 7.81 (d, J = 7.9 Hz, 1 H), 8.17-8.21 (m, 1 H), 8.28-8.32 (m, 1 H);
MS m/e 448 (MH^+).



142

Compound **142** was prepared using the same procedure as compound **141**. Excess electrophile was scavenged by the addition of PS-thiophenol resin (Argonaut, 100 mg), which was stirred with the reaction mixture for 4 hours. Purification by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) gave 0.012 g (19 % yield) of a trifluoroacetic acid salt of compound **142** as an off-white solid:

^{1}H NMR (DMSO-d_6) δ 1.51-1.56 (m, 2 H), 1.85-1.91 (m, 2 H), 3.45 (t, J = 6.3 Hz, 2 H), 4.50 (t, J = 7.4 Hz, 2 H), 4.74-4.83 (m, 2 H), 4.81 (dt, J = 2.6, 83.1 Hz, 2 H), 7.20-7.22 (m, 1 H), 7.36-7.37 (m, 1 H), 7.41-7.44 (m, 1 H), 7.63 (d, J = 8.0 Hz, 1 H), 7.81 (d, J = 7.9 Hz, 1 H), 8.24-8.27 (m, 2 H);
MS m/e 412 (MH^+).

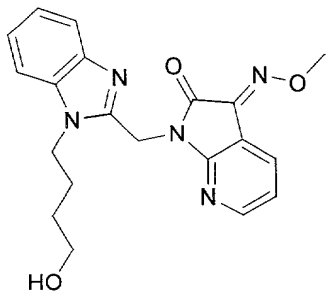


143

Compound **143** was prepared by the same procedure as described for the preparation of compound **141**. Excess electrophile was scavenged by the addition of PS-thiophenol resin (Argonaut, 100 mg), which was stirred with the reaction mixture for 4 hours. Purification by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) gave a mixture of

compound **143** plus the trifluoroacetate ester of compound **143**. This mixture was dissolved in methanol and the resulting solution was treated with MP-carbonate resin (Argonaut) for 18 hours at room temperature. Filtration to remove the resin followed by concentration of the filtrate *in vacuo* gave 0.022 g (34 % yield) of compound **143** as a yellow glassy solid:

^{1}H NMR (DMSO-d_6) δ 1.48-1.51 (m, 2 H), 1.81-1.84 (m, 2 H), 3.24 (s, 3 H), 3.43-3.45 (m, 2 H), 4.36 (t, J = 7.3 Hz, 2 H), 4.50 (t, J = 5.1 Hz, 1 H), 5.25 (s, 2 H), 5.68 (s, 2 H), 7.12 (t, J = 8.0 Hz, 1 H), 7.17-7.22 (m, 2 H), 7.47 (d, J = 8.0 Hz, 1 H), 7.56 (d, J = 8.1 Hz, 1 H), 7.76 (d, J = 8.3 Hz, 2 H), 7.99 (d, J = 8.3 Hz, 2 H), 8.26-8.28 (m, 2 H);
MS m/e 534 (MH^+).



144

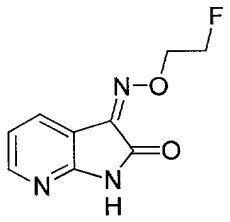
A mixture of compound **140** (0.050 g, 0.12 mmol) with cesium carbonate (0.12 g, 0.37 mmol) and iodomethane (0.019 g, 0.14 mmol) in anhydrous CH_3CN (3 mL) was stirred for 18 hours at room temperature. The mixture became a deep olive green color during the course of the reaction. MeOH (1 mL) was added to remove the acetate group, and excess iodomethane was scavenged by the addition of PS-thiophenol resin (Argonaut, 100 mg) which was stirred with the reaction mixture for 2 hours. Solids were removed by filtration and rinsed with MeOH and the filtrate was concentrated *in vacuo* to a green solid. Purification of the crude product by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) gave a mixture of compound **144** plus the trifluoroacetate ester of compound **144**. This mixture was dissolved in MeOH and the resulting solution was treated with MP-carbonate resin (Argonaut)

for 18 hours at room temperature. Filtration to remove the resin followed by concentration of the filtrate *in vacuo* gave 0.007 g (16% yield) of compound **144** as a yellow glassy solid:

^{1}H NMR (DMSO-d_6) δ 1.49-1.52 (m, 2H), 1.81-1.84 (m, 2H), 3.43-3.46 (m, 2H), 4.28 (s, 3H), 4.37 (t, J = 7.4 Hz, 2H), 4.51 (t, J = 5.1 Hz, 1H), 5.27 (s, 2H), 7.11-7.17 (m, 2H), 7.20-7.23 (m, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 8.20 (dd, J = 1.6, 7.4 Hz, 1H), 8.25 (dd, J = 1.6, 5.3 Hz, 1H);
MS m/e 380 (MH^+).

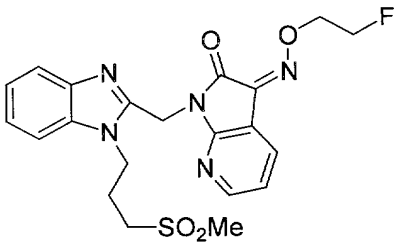
O-(2-Fluoro-ethyl)-hydroxylamine was prepared using a procedure described by Ishikawa, et al *J. Antibiot.*, **2000**, *53*, 1071.

1H-Pyrrolo[2,3-b]pyridine-2,3-dione 3-[O-(2-fluoro-ethyl)-oxime]



A solution of compound **134a** (300 mg, 1.03 mmol) in DMSO (25 mL) was heated at 95^{0}C at 15 torr for 6.5 hours. The solution containing the corresponding 7-aza isatin was cooled to room temperature, followed by the addition O-(2-Fluoro-ethyl)-hydroxylamine hydrochloride (131 mg, 1.13 mmol). After stirring for 1 hour at room temperature the mixture was quenched with water and extracted with ethyl acetate (6 x 25 mL). The combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (gradient, 2% MeOH in methylene chloride to 3%) to give 1H-Pyrrolo[2,3-b]pyridine-2,3-dione 3-[O-(2-fluoro-ethyl)-oxime] (200 mg, 93%) as an orange solid that was further purified by trituration from diethyl ether-methylene chloride (1:1).

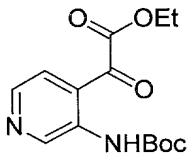
^{1}H NMR ($CDCl_3$) δ do 3.48 (s, 3 H), 4.97 (s, 2 H), 7.40-7.50 (m, 2 H), 7.75-7.85 (m, 2 H);
MS m/e 209 (MH^+).



145

Compound **145** was prepared according the procedure for the preparation of compound **134**, starting from 1H-pyrrolo[2,3-b]pyridine-2,3-dione 3-[O-(2-fluoro-ethyl)-oxime] (18.9 mg, 0.0904 mmol) and **10d** (29.2 mg, 0.0904 mmol). Purification was accomplished by trituration from methylene chloride-methanol) to give compound **145** (18 mg, 43% yield) as a yellow solid.
^{1}H NMR (DMSO) δ 8.26 (dd, J = 1.6, 5.3 Hz, 1H), 8.23 (dd, J = 1.6, 7.5 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 7.8 Hz, 1H), 7.18 (dd, J = 7.5, 5.3 Hz, 1H), 7.14 (t, J = 7.9 Hz, 1 H), 5.30 (s, 2 H), 4.72-4.90 (m, 4H), 4.52 (t, J = 7.4 Hz, 2H), 3.30 (t, J = 7.5 Hz, 2H), 3.02 (s, 3H), 2.28 (m, 2H);
MS m/e 460 (MH^+).

(3-tert-Butoxycarbonylamino-pyridin-4-yl)-oxo-acetic acid ethyl ester



146

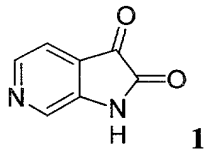
(3-tert-Butoxycarbonylamino-pyridin-4-yl)-oxo-acetic acid ethyl ester was prepared according to a procedure described by Estel, etc (*J. Heterocycl. Chem.*, **1989**, *26*, 105-): To a solution of pyridin-3-yl-carbamic acid tert-butyl ester (8.50 g, 43.8 mmol) and TMEDA (16.5 mL, 109 mmol) in THF (200 mL) at –78^{0}C was cannulated *tert.*-BuLi (64.1 mL, 1.7 M in pentane) over 30 min under

nitrogen. The mixture was then stirred for 2 hours between –10^{0}C and –20^{0}C. After cooling to –60^{0}C diethyl oxalate (17.8 mL, 131 mmol) was added and the mixture allowed to warm to 0^{0}C. After 3 hours the mixture was poured onto ice/1M HCl (120 mL) and extracted with ethyl acetate (3x150 mL). The combined organic extracts were washed with water (100 mL), brine (75 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (gradient, hexane/ethyl acetate 5:2, 2:1), to give 3.04 g (24% yield) of compound **146** as a yellow oil.

^{1}H NMR (DMSO) δ 9.80 (s, 1H), 9.70 (br s, 1H), 8.40 (d, J 5.2 Hz, 1H), 7.50 (d, J = 5.2 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H);

MS m/e 327 (M^+-$MeOH^+$).

1H-Pyrrolo[2,3-c]pyridine-2,3-dione



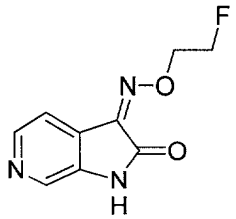
147

Compound **146** (1.62 g, 5.50 mmol) was heated for 7 min at 180-190^{0}C in a kugelrohr oven at 15 torr. The remaining black solid **147** (823 mg) was used without further purification.

^{1}H NMR (DMSO) δ 11.2 (s, 1H), 8.45 (br s, 1H), 8.34 (br s, 1H), 7.41 (br s, 1H);

MS m/e 180 (M^+-$MeOH^+$).

1H-Pyrrolo[2,3-c]pyridine-2,3-dione 3-[O-(2-fluoro-ethyl)-oxime]



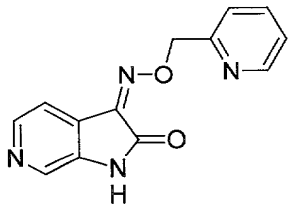
148a

1H-Pyrrolo[2,3-c]pyridine-2,3-dione (208 mg, 1.40 mmol) was dissolved in DMSO (5 mL) and treated with O-(2-Fluoro-ethyl)-hydroxylamine (243 mg, 2.11 mmol). After stirring for 1 hour at room temperature, water (30 mL) was added and the mixture extracted with ethyl acetate (6x20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The residue was triturated from diethyl ether to give 130 mg (44% yield over 2 steps) of **148a** as a yellow solid.

^{1}H NMR (DMSO) δ 11.0 (s, 1H), 8.40 (d, J = 4.8 Hz, 1H), 8.28 (s, 1H), 7.73 (d, J = 4.7 Hz, 1H), 4.69 – 4.87 (m, 4H);

MS m/e 210 (MH^+).

1H-Pyrrolo[2,3-c]pyridine-2,3-dione 3-(O-pyridin-2-ylmethyl-oxime)



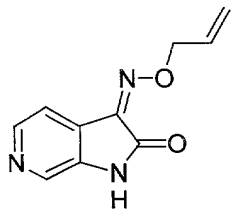
148b

1H-Pyrrolo[2,3-c]pyridine-2,3-dione (110 mg, 0.743 mmol) was dissolved in DMSO (4 mL) and treated with O-pyridin-2-ylmethyl-hydroxylamine (176 mg, 0.892 mmol). After stirring for 1 hour at room temperature, DIPEA (129 µL, 0.743 mmol) was added and the mixture heated to 60^{0}C and stirred for 2 hours at the same temperature. The mixture was cooled to room temperature, water (20 mL) was added and the mixture extracted with ethyl acetate (7x15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (6% methanol in methylene chloride), to give 45 mg (24% yield over 2 steps) of **148b** as a yellow solid.

^{1}H NMR ($CDCl_3$) δ 9.98 (s, 1H), 8.63 (d, J = 4.6 Hz, 1H), 8.42 (d, J = 4.8 Hz, 1H), 8.38 (s, 1H), 7.77 (d, J = 4.6 Hz, 1H), 7.73 (t, J = 7.7 Hz, 1 H), 7.43 (d, J = 7.8 Hz, 1H), 7.28 (dd, J = 4.8, 7.4 Hz, 1H);

MS m/e 255 (MH^+);

1H-Pyrrolo[2,3-c]pyridine-2,3-dione 3-(O-allyl-oxime)

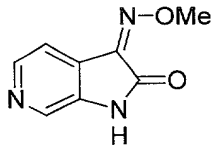


148c

Compound **147** (121 mg, 0.817 mmol) was dissolved in a mixture of MeCN (4 mL) and water (2 mL), and treated with O-Allyl-hydroxylamine (99 mg, 0.90 mmol). After stirring for 75 min at room temperature, another 50 mg of the O-Allyl-hydroxylamine was added. After 30 min. MeCN was stripped off and the residue extracted with ethyl acetate (7x15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The resulting yellow solid **148c** (80 mg, 48% over two steps) was sufficiently pure for the next step.

^{1}H NMR (DMSO) δ 11.0 (s, 1H), 8.39 (d, J = 4.8 Hz, 1H), 8.27 (s, 1H), 7.70 (d, J 4.8 Hz, 1H), 6.10 (m, 1H), 5.43 (d, J = 17.3 Hz, 1H), 5.34 (d, J = 10.5 Hz, 1H), 5.00 (d, J = 5.8 Hz, 1H).

1H-Pyrrolo[2,3-c]pyridine-2,3-dione 3-(O-methyl-oxime)

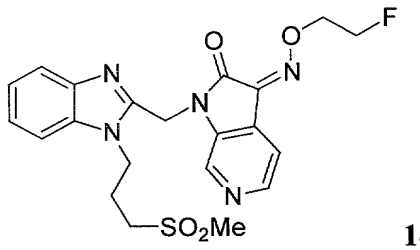


148d

Compound **147** (154 mg, 1.04 mmol) was dissolved in a mixture of MeCN (4 mL) and water (2 mL), and treated with O-methyl-hydroxylamine (96 mg, 1.1 mmol). After stirring for 75 min at room temperature, another 48 mg of the O-methyl-hydroxylamine was added. After 30 min. the solvents were evaporated and the residue purified by flash column chromatography (gradient, 5, 6, 7%

methanol in methylene chloride), to give 52 mg (28% yield over 2 steps) **148d** as a yellow solid.

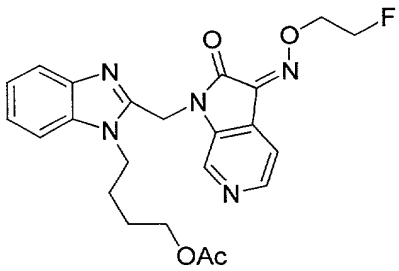
^{1}H NMR (DMSO) δ 11.0 (s, 3H), 8.37 (d, J = 4.7 Hz, 1H), 8.27 (s, 1H), 7.70 (d, J = 4.8 Hz, 1H), 4.26 (s, 3H);



148

Compound **148** was prepared according the procedure for the preparation of compound **134**, starting from isatin **148a** (19.9 mg, 0.0952 mmol) and **10d** (30.8 mg, 0.0952 mmol). Purification was accomplished by preparative TLC (eluens 5% methanol in methylene chloride) to give compound **148** (25 mg, 57% yield) as a yellow solid.

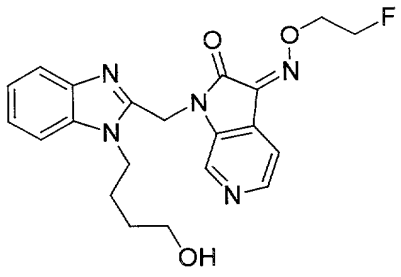
^{1}H NMR (DMSO) δ 8.26 (dd, J = 1.6, 5.3 Hz, 1H), 8.23 (dd, J = 1.6, 7.5 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 7.8 Hz, 1H), 7.18 (dd, J = 7.5, 5.3 Hz, 1H), 7.14 (t, J = 7.9 Hz, 1H), 5.30 (s, 2H), 4.72-4.90 (m, 4H), 4.52 (t, J = 7.4 Hz, 2H), 3.30 (t, J = 7.5 Hz, 2H), 3.02 (s, 3H), 2.28 (m, 2H);
MS m/e 460 (MH^+);



149

Compound **149** was prepared according the procedure for the preparation of compound **134**, starting from isatin **148a** (28.6 mg, 0.137 mmol) and **139a** (43.4 mg, 0.137 mmol). The product **149** was used as it is.

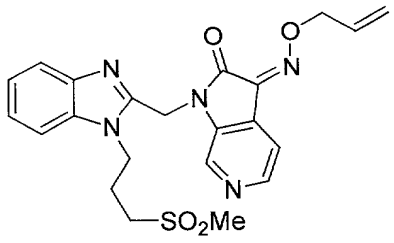
^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.49 (d, J = 4.8 Hz, 1H), 7.76 (m, 2H), 7.30 (m, 2H), 5.30 (s, 2H), 4.75 - 4.85 (m, 4H), 4.30 (t, J = 7.2 Hz, 2H), 4.05 (t, J = 6.3 Hz, 2 H), 1.98 (s, 3H), 1.76 (m, 4H);
MS m/e 453 (MH^+).



150

Compound **149** (0.137 mmol, assuming quantitative recovery) was dissolved in methanol (3 mL) and 5 drops of thionyl chloride were added. The solution was stirred overnight and the volatiles evaporated. The residue was redissolved in methanol and concentrated. This procedure was repeated three times. Purification was accomplished by preparative TLC (eluant 5% methanol in methylene chloride) to give compound **150** (27 mg, 48% yield over two steps) as a yellow solid.

^{1}H NMR (DMSO) δ 8.57 (s, 1H), 8.49 (d, J = 4.8 Hz, 1H), 7.83 (d, J = 4.8 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.24 (t, J = 7.4 Hz, 1H), 7.17 (t, J = 7.3 Hz, 1H), 5.35 (s, 2H), 4.76 - 4.90 (m, 4H), 4.48 (t, J = 5.2 Hz, 1H), 4.34 (t, J = 7.4 Hz, 2H), 3.43 (q, J = 6.3 Hz, 2H), 1.77 (m, 2H), 1.49 (m, 2H);
MS m/e 412 (MH^+).

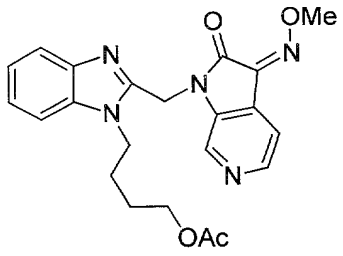


151

Compound **151** was prepared according the procedure for the preparation of compound **134**, starting from isatin **148c** (84 mg, 0.41 mmol) and **10d** (134 mg, 0.41 mmol). Purification was accomplished by flash column chromatography (eluent 5% methanol in methylene chloride), to give 118 mg (63% yield) of compound **151** as a yellow solid.

^{1}H NMR (DMSO) δ 8.61 (s, 1H), 8.48 (d, J = 4.8 Hz, 1H), 7.80 (d, J = 4.8 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.56 (d, J 8.0 Hz, 1 H), 7.28 (t, J 8.0 Hz, 1 H), 7.17 (t, J 8.0 Hz, 1H), 6.13 (m, 2H), 5.46 (d, J = 17.3 Hz, 1H), 5.36 (d, J = 10.5 Hz, 1H), 5.37 (s, 2H), 5.06 (d, J = 5.8 Hz, 2 H), 4.48 (t, J 7.5 Hz, 2H), 3.26 (t, J = 7.6 Hz, 2H), 3.02 (s, 3H), 2.22 (m, 2H);

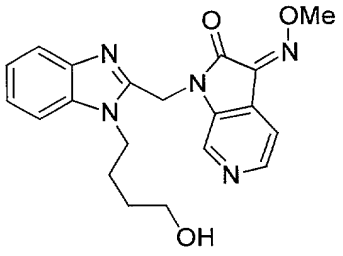
MS m/e 454 (MH^+);



152

Compound **152** was prepared according the procedure for the preparation of compound **134**, starting from isatin **148d** (14.3 mg, 0.0807 mmol) and **139a** (25.6 mg, 0.0807 mmol). The product was used as it is.

MS m/e 422 (MH^+).

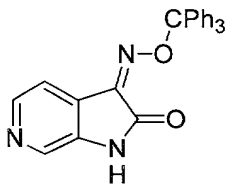


153

Compound **153**(0.0807 mmol, assuming quantitative recovery) was dissolved in methanol (2 mL) and acetyl chloride (58 μL) was added. The

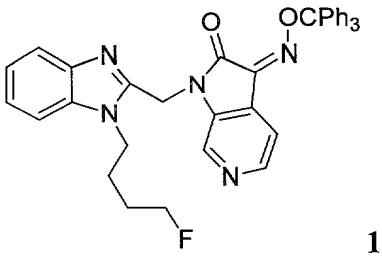
solution was stirred for 5 hours and the volatiles evaporated. The residue was redissolved in methanol and concentrated. This procedure was repeated three times. Purification was accomplished by flash column chromatography (eluent 6% methanol in methylene chloride), to give 9 mg (29% yield) of compound **153** as a yellow solid, which was converted into the HCl salt by dissolution in methanol and addition of 4N HCl in dioxane (6 μL), followed by concentration.
^{1}H NMR ($CDCl_3$) δ 8.95 (s, 1H), 8.49 (d, J = 4.8 Hz, 1H), 7.77 (m, 1H), 7.23 (d, J = 4.5 Hz, 1H), 7.33 (m, 3H), 5.35 (s, 2H), 4.39 (s, 3H), 4.33 (m, 2H) 3.69 (t, J = 6.1 Hz, 2H), 1.82 (m, 2H), 1.67 (m, 2H);
MS m/e 380 (MH^+).

1H-Pyrrolo[2,3-c]pyridine-2,3-dione 3-(O-trityl-oxime)



154a

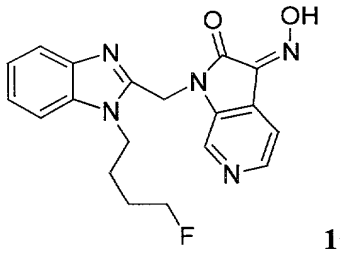
1H-Pyrrolo[2,3-c]pyridine-2,3-dione (298 mg, 2.01 mmol) was dissolved in DMSO (4 mL) and treated with O-Trityl-hydroxylamine (609 mg, 2.21 mmol). After stirring for 20 min. at room temperature, the temperature was raised to 70^{0}C and 30 min.later to 100^{0}C, and stirring was continued for 2 hours. After cooling to room temperature, water (30 mL) was added and the mixture extracted with ethyl acetate (2x50 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated. Purification was accomplished by flash column chromatography (eluent 5% methanol in methylene chloride), to give 130 mg (13% yield) **154a** as a yellow oil.
^{1}H NMR ($CDCl_3$) δ 9.57 (br s, 1H), 8.47 (d, J = 4.8 Hz, 1H), 8.31 (s, 1H), 7.94 (d, J = 4.8 Hz, 1H), 7.32 (m, 15H);
MS m/e 406 (MH^+).



154

Compound **154** was prepared according the procedure for the preparation of compound **134**, starting from **154a** (121 mg, 0.298 mmol) and **132c** (83 mg, 0.298 mmol). The residue after work-up was precipitated from diethyl ether to give **154** (114 mg) as a yellow solid. The rest was purified by flash column chromatography (eluent 3%, 5% methanol in methylene chloride), to give 13 mg of **154** for a combined yield of 127 mg (70%).

^{1}H NMR ($CDCl_3$) δ 8.94 (s, 1H), 8.52 (d, J = 4.7 Hz, 1 H), 8.93 (d, J = 4.7 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.35 (m, 18H), 5.31 (s, 2H), 4.25 – 4.28 (m, 4H), 1.69 (m, 4H).

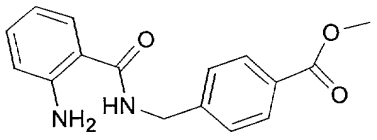


155

To a solution of **154** (127 mg, 0.208 mmol) in acetonitrile (3 mL) and methylene chloride (1 mL) was added *p*-TsOH.H_2O (59 mg, 0.312 mmol). The mixture was heated in a sealed tube at 100^{0}C for 10 min. The solvents were removed *in vacuo* and the residue purified by flash column chromatography (eluent 3%, 5%, 8%, 10%, 15% methanol in methylene chloride), to give 58 mg (68%) of **155**, that was converted into the HCl salt by dissolving in methanol and addition of excess acetyl chloride. The product was a single configurational isomer in DMSO-d6 (*Z*-isomer), but was a 5:1 mixture in methanol (CD_3OD).

^{1}H NMR (CD_3OD) δ 8.97 (s, 1H), 8.76 (d, J = 5.7 Hz, 1 H), 8.62 (d, J = 5.7 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.69 (t, J = 7.3 Hz, 1H), 7.64 (t, J = 7.3 Hz, 1H), 5.86 (s, 2H), 4.71 (t, J = 7.9 Hz, 2H), 4.57 (dt, J = 5.8, 47 Hz, 2H), 2.18 (m, 2H), 1.94 (m, 2H);

MS m/e 368 (MH^+).



156a

A solution of anthranilic acid (1.66 g, 12.10 mmol), hydroxybenztriazole (1.64 g, 12.10 mmol), and methyl 4-(methylamino)benzoate (2.0 g, 12.10 mmol) in DMF (20 mL) was treated with EDAC (2.32 g, 12.10 mmol) and the mixture was stirred at room temperature for 12 hours. The solvent was removed and the residue was dissolved in EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 5:1) to give 2.05 g (59% yield) of compound **156a** as a white solid:

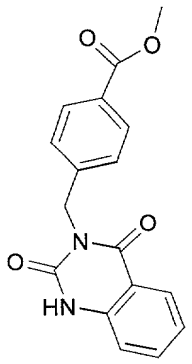
^{1}H NMR (DMSO-d_6) δ 3.82 (s, 3 H), 4.49 (d, J = 5.9 Hz, 2 H), 4,58 (d, J = 5.9 Hz, 2 H), 6.44-6.59 (m, 3 H), 6.70 (d, J = 8.2 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1 H), 7.13-7.22 (m, 2 H), 7.44 (d, J = 8.2 Hz, 2 H), 7.48 (d, J = 8.2 Hz, 2 H), 7.57 (d, J = 6.9 Hz, 2 H), 7.88-7.94 (m, 2 H), 8.55 (d, J = 8.3 Hz, 1 H), 8.86 (t, J = 5.9 Hz, 1 H), 9.46 (t, J = 5.9 Hz, 1 H);

IR (KBr, cm^{-1}) 1706, 1654, 1528;

MS m/e 284 (MH^+);

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85

Found: C, 67.87; H, 5.63; N, 9.87.



156b

To a mixture of compound **156a** (2.0 g, 7.04 mmol) and $KHCO_3$ (1.74 g, 17.30 mmol) in H_2O (50 mL) was added methyl chloroformate (1.09 ml, 14.00 mmol) and the mixture was stirred for 12 hours at room temperature. The resulting solid was isolated by filtration to give 2.4 g (99% yield) of the intermediate as a white solid. The solid was dissolved in MeOH (100 mL), treated with sodium methoxide (0.5 M, 1.0 mL) and heated to reflux for 4 hours. The precipitated product was isolated by filtration to give 1.58 g (73% yield) of compound **156b** as a white solid:

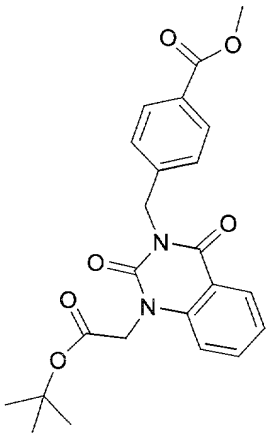
^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3 H), 5.16 (s, 2 H), 7.23 (t, J = 6.9 Hz, 1 H), 7.43 (d, J = 8.4 Hz, 1 H), 7.72 (t, J = 7.5 Hz, 1 H), 7.69-7.96 (m, 4 H);

IR (KBr, cm^{-1}) 1718, 1656;

MS m/e 310 (MH^+);

Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03

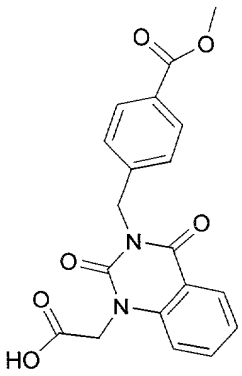
Found: C, 65.77; H, 4.81; N, 8.83.



156c

A solution of compound **156b** (3.2 g, 10.3 mmol) and K_2CO_3 (2.84 g, 20.3 mmol) in CH_3CN (100 mL) was treated with *t*-butyl bromoacetate (2.0 g, 10.3 mmol) and stirred at room temperature for 12 hours. The mixture was filtered and the filtrate was concentrated. The residue was purified by flash chromatography (20% EtOAc in hexanes) to give 4.3 g (99% yield) of compound **156c** as a clear oil:

^{1}H NMR (DMSO-d_6) δ 1.20 (t, J = 7.2 Hz, 3 H), 1.41 (s, 9 H), 1.15 (q, J = 7.2 Hz, 2 H), 4.72 (s, 2 H), 4.90 (s, 2 H), 7.31-7.37 (m, 1 H), 7.42 (d, J = 8.5 Hz, 3 H), 7.78-7.85 (m, 1 H), 7.88 (d, J = 8.5 Hz, 2 H), 8.10 (d, J = 6.3, 1 H);
IR (KBr, cm^{-1}) 1746, 1712, 1669;
MS m/e 362 (MH^+);
Anal. Calcd for $C_{18}H_{22}N_2O_6 \bullet 1.33\ H_2O$: C, 61.61; H, 5.99; N, 6.25
Found: C, 61.21; H, 5.59; N, 5.91.



156d

A solution of compound **156c** (5.5 g, 14.1 mmol) in TFA (50 mL) was stirred at room temperature for 12 hours. The mixture was concentrated to give 4.3 g (99% yield) of compound **156d** as a white solid:

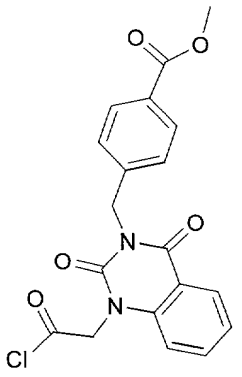
^{1}H NMR (DMSO-d_6) δ 3.82 (s, 3 H), 4.88 (s, 2 H), 5.21 (s, 2 H), 7.33 (t, J = 7.8 Hz, 1 H), 7.42 (d, J = 8.4 Hz, 3 H), 7.88 (t, J = 7.5 Hz, 1 H), 7.92 (d, J = 7.5 Hz, 2 H), 8.09 (d, J = 7.8 Hz, 1 H);

IR (KBr, cm^{-1}) 1712, 1664;

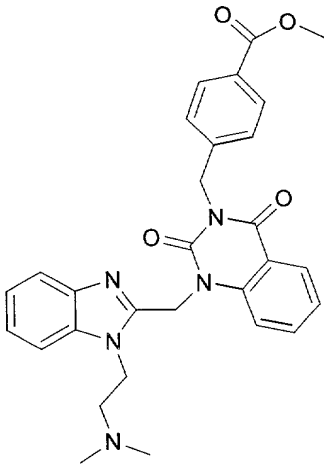
MS m/e 368 (MH^+);

Anal. Calcd for $C_{19}H_{16}N_2O_6 \bullet 0.94\ H_2O$: C, 59.24; H, 4.68; N, 7.27

Found: C, 59.24; H, 4.45; N, 6.88.



156e



156

A solution of compound **156d** (0.5 g, 1.36 mmol) was heated to reflux in thionyl chloride (10 mL) for 30 minutes then cooled and concentrated to give the acid chloride **156e**. The compound **98b** (0.24 g, 1.36 mmol) was dissolved in CH_2Cl_2 (20 mL), cooled to -78°C and treated with the acid chloride **156e** in CH_2Cl_2 (20 mL). The mixture was warmed to room temperature and stirred for 12 hours. The organic layer was washed with saturated aqueous $NaHCO_3$, dried, and concentrated. The residue was purified by flash chromatography (CH_2Cl_2 : MeOH = 20:1) to give 0.42 g (49% yield) of a yellow oil. The oil was dissolved in AcOH (50 mL) and heated to reflux for 2 hours then cooled. The excess acetic acid was removed and the residue purified by flash chromatography (CH_2Cl_2 : MeOH = 97:3) to give 0.28 g (70% yield) of compound **156** as a white solid:

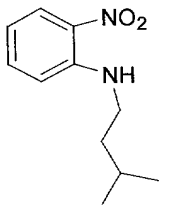
^{1}H NMR (DMSO-d_6) δ 2.95 (s, 6 H), 3.49-3.62 (m, 2 H), 3.83 (s, 3 H), 4.73-4.80 (m, 2 H), 5.26 (s, 2 H), 5.79 (s, 2 H), 7.26 (t, J = 7.5 Hz, 1 H), 7.36-7.40 (m, 2 H), 7.48 (d, J = 7.5 Hz, 2 H), 7.54-7.64 (m, 2 H), 7.65-7.81 (m, 2 H), 7.90 (d, J = 7.5 Hz, 2 H), 8.15 (d, J = 7.5 Hz, 1 H);

IR (KBr, cm^{-1}) 1711, 1667, 754;

MS m/e 511 (MH^+);

Anal. Calcd for $C_{29}H_{29}N_5O_4 \bullet 0.97\ H_2O$: C, 50.16; H, 4.14; N, 8.60

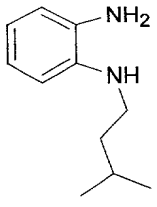
Found: C, 50.16; H, 3.74; N, 8.23.



157a

A solution of 2-fluoronitrobenzene (20 g, 142 mmol) and 3-methylbutylamine (12.4 g, 142 mmol) in CH_3CN (100 mL) and Et_3N (28.5 g, 282 mmol) was heated to reflux for 5 days, then cooled and concentrated. The residue was dissolved in EtOAc and washed with 1N HCl. The mixture was dried over $MgSO_4$ and concentrated to give 27.5 g (93% yield) of compound **157a** as a dark orange oil:

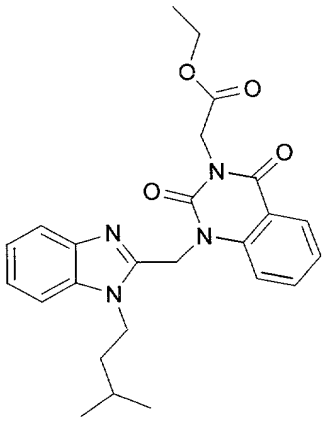
^{1}H NMR ($CDCl_3$) δ 0.96 (d, J = 6.5 Hz, 6 H), 1.64 (q, J = 7.3 Hz, 2 H), 1.65-1.82 (m, 1 H), 3.26-3.32 (m, 2 H), 6.61 (t, J = 8.3 Hz, 1 H), 6.83 (d, J = 8.4 Hz, 1 H), 7.42 (t, J = 8.0 Hz, 1 H), 8.05 (bs, 1 H, exchanges with D_2O), 8.15 (d, J = 8.7 Hz, 1 H);
MS m/e 208 (MH^+).



157b

A solution of compound **157a** (6.1 g, 29.3 mmol) in EtOH (50 mL) was reduced by catalytic hydrogenation at 40 psi with 10% palladium on carbon (100 mg) for 4 hours. The catalyst was removed by filtration and the solvent was evaporated to give 5.0 g (99% yield) of compound **157b** as a dark oil:

^{1}H NMR (DMSO-d_6) δ 0.91 (d, J = 6.7 Hz, 6 H), 1.47 (q, J = 7.0 Hz, 2 H), 3.00 (t, J = 7.2 Hz, 2 H), 3.28-3.50 (m, 2 H), 6.37-6.46 (m, 2 H), 6.47-6.53 (m, 2 H);
MS m/e 178 (MH^+).



157

Compound **157** was prepared using the same procedures as compound **156** with compounds **157b** and **156e**:

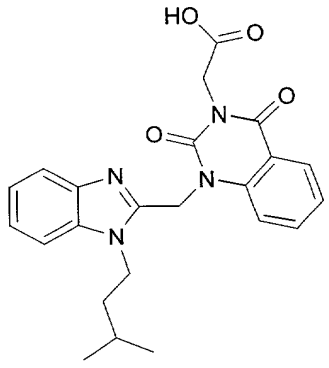
^{1}H NMR (DMSO-d_6) δ 1.00 (d, J = 6.0 Hz, 6 H), 1.20 (t, J = 7.2 Hz, 3 H), 1.63-1.78 (m, 2 H), 4.15 (q, J = 6.9 Hz, 2 H), 4.36 (t, J = 7.5 Hz, 2 H), 4.76 (s, 2 H), 5.70 (s, 2 H), 7.11 (t, J = 7.5 Hz, 1 H), 7.21 (t, J = 7.5 Hz, 1 H), 7.17 (t, J = 7.5 Hz, 1 H), 7.46 (d, J = 7.5 Hz, 1 H), 7.50-7.60 (m, 2 H), 7.78 (t, J = 7.5 Hz, 1 H), 8.18 (d, J = 7.5 Hz, 1 H);

IR (KBr, cm^{-1}) 1742, 1709, 1669, 740;

MS m/e 448 (MH^+);

Anal. Calcd for $C_{25}H_{28}N_4O_4$: C, 66.95; H, 6.29; N, 12.49

Found: C, 66.76; H, 6.14; N, 12.28.



158

A mixture of compound **157** (390 mg, 0.87 mmol) and 1N NaOH (0.88 ml, 0.88 mmol) in MeOH (50 mL) was heated to reflux for 4 hours to give a clear solution. The mixture was concentrated and the residue dissolved in 1N HCl and filtered to give 303 mg (83% yield) of compound **158** as a white solid:

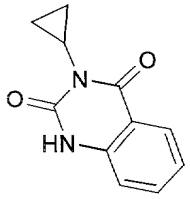
^{1}H NMR (DMSO-d_6) δ 0.99 (d, J = 5.7 Hz, 6 H), 1.65-1.82 (m, 2 H), 4.25-4.60 (m, 2 H), 4.67 (s, 2 H), 5.88 (s, 2 H), 7.35-7.58 (m, 3 H), 7.48 (t, J = 7.5 Hz, 2 H), 7.79 (t, J = 7.5 Hz, 2 H) 8.16 (d, J = 7.5 Hz, 1 H);

IR (KBr, cm^{-1}) 1711, 1669, 757;

MS m/e 420 (MH^+);

Anal. Calcd for $C_{23}H_{24}N_4O_4 \bullet H_2O$: C, 60.97; H, 6.14; N, 12.37

Found: C, 60.59; H, 5.74; N, 12.18.



159a

Compound **159a** was prepared using the same procedure as compound **156b** starting with cyclopropylamine:

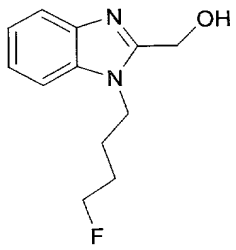
^{1}H NMR (DMSO-d_6) δ 0.70-0.74 (m, 2 H), 0.98-1.02 (m, 2 H), 2.61-2.65 (m, 1 H), 7.11-7.18 (m, 2 H), 7.61 (t, J = 7.5 Hz, 1 H), 7.89 (d, J = 7.9 Hz, 1 H);

IR (KBr, cm^{-1}) 1727, 1666, 1163, 1082;

MS m/e 202 (MH^+);

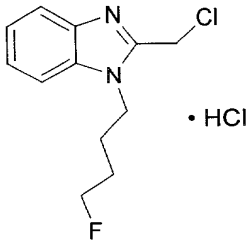
Anal. Calcd for $C_{11}H_{10}N_2O_2 \bullet 0.4\ H_2O$: C, 63.29; H, 5.18; N, 13.42

Found: C, 63.55; H, 5.44; N, 13.02.



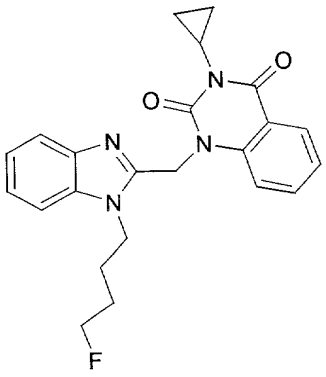
159b

To a solution of 2-hydroxymethylbenzimidazole (1.5 g, 10.12 mmol) in a mixture of DMF and THF (60 mL, 1:1) was added sodium hydride (60% suspension in mineral oil, 425 mg, 10.63 mmol). After stirring for 1 hour at room temperature, 1-bromo-4-fluorobutane (1.56 g, 10.12 mmol) was added and the reaction was stirred at 65 °C for 18 hours. The solvent was evaporated. The residue was diluted with 1N NaOH and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and evaporated to give 2.34 g (quantitative yield) of compound **159b** as a yellow oil which was used without further purification.



159c

To solution of alcohol **159b** (2.30 g, 10.34 mmol) in CH_2Cl_2 (30 mL) was added thionyl chloride (2.46 g, 20.68 mmol) at 0 °C. The reaction was stirred for 2 hours and then the solvent and excess thionyl chloride were evaporated to give 2.8 g (98% yield) of compound **159c**.



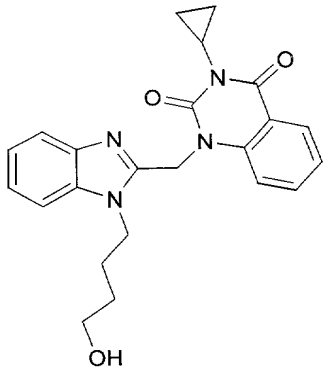
159

Compound **159** was prepared using the same procedure as compound **4** with compound **159a** and compound **159c**:

^{1}H NMR (DMSO-d_6) δ 0.73-0.76 (m, 2 H), 1.03-1.09 (m, 2 H), 1.73-1.83 (m, 2 H), 1.86-1.93 (m, 2 H), 2.74-2.79 (m, 1 H), 4.42 (t, J = 7.5 Hz, 2 H), 4.47 (t, J = 6.0 Hz, 2 H), 4.52 (t, 5.1 Hz, 1 H), 5.62 (s, 2 H), 7.11 (t, J = 7.2 Hz, 1 H), 7.22 (t, J = 8.0 Hz, 1 H), 7.23 (t, J = 7.5 Hz, 1 H), 7.27 (t, J = 7.5 Hz, 1 H), 7.47-7.49 (m, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.66 (t, J = 7.6 Hz, 1 H), 8.06 (d, J = 8.0 Hz, 1 H); MS m/e 406 (MH^+);

Anal. Calcd for $C_{23}H_{23}FN_4O_2$: C, 67.96; H, 5.70; N, 13.78

Found: C, 67.57; H, 5.51; N, 13.67

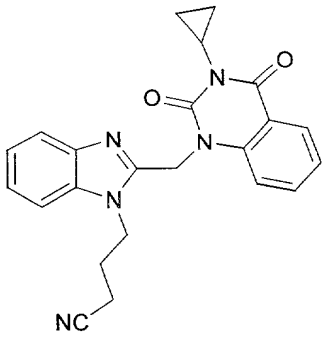


160

To a solution of compound **159a** (127 mg, 0.63 mmol) in THF (20 mL) was added BTPP (0.6 mL, 1.98 mmol) and the mixture was stirred for 30 minutes at room temperature. Compound **139a** (200 mg, 0.63 mmol) was added and the

mixture was stirred for 12 hours at room temperature. The solvent was removed. The residue was dissolved in MeOH (5 mL) and diluted with diethyl ether (20 mL) and water (50 mL). After standing for 30 minutes, the precipitated product was isolated by filtration to give 214 mg (84% yield) of compound **160** as a white solid:

^{1}H NMR (DMSO-d_6) δ 0.73-0.76 (m, 2H), 1.03-1.09 (m, 2H), 1.50-1.56 (m, 2H), 1.79-1.86 (m, 2H), 2.75-2.79 (m, 1H), 3.46 (q, J = 6.3 Hz, 2H), 4.39 (t, J = 7.4 Hz, 2H), 4.52 (t, J = 5.1 Hz, 2H), 5.62 (s, 2H), 7.11 (t, J = 7.2 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1 H), 7.27 (t, J = 7.5 Hz, 1H), 7.47-7.49 (m, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H);
IR (KBr) 1702, 1664, 1607, 1481;
MS m/e 404 (MH^+);
Anal. Calcd for $C_{23}H_{24}N_4O_3$: C, 68.30; H, 5.98; N, 13.85
Found: C, 67.99; H, 6.06; N, 13.92.



161

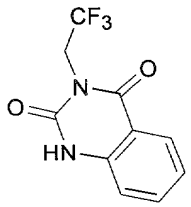
Compound **161** was prepared using the same method as compound **160** with compound **159a** and compound **25b**:

^{1}H NMR (DMSO-d_6) δ 0.72-0.75 (m, 2H), 1.02-1.06 (m, 2H), 2.14-2.20 (m, 2H), 2.69 (t, J = 7.4 Hz, 2H), 2.74-2.78 (m, 1H), 4.44 (t, J = 7.5 Hz, 2H), 5.63 (s, 2H), 7.13 (t, J = 7.9 Hz, 1H), 7.22-7.30 (m, 2H), 7.48-7.53 (m, 2H), 7.61 (d, J = 8.1Hz, 1H), 7.68 (t, J = 7 Hz, 1H), 8.06 (d, J = 7.5 Hz, 1H);
IR(KBr) 1708, 1667, 1608;

MS m/e 399 (MH^+);

Anal. Calcd for $C_{23}H_{21}N_5O_2$: C, 69.15; H, 5.29; N, 17.53

Found: C, 69.36; H, 5.20; N, 17.56.



162a

Compound **162a** was prepared using the same procedure as compound **156b** starting with 2,2,2-trifluoroethylamine hydrochloride:

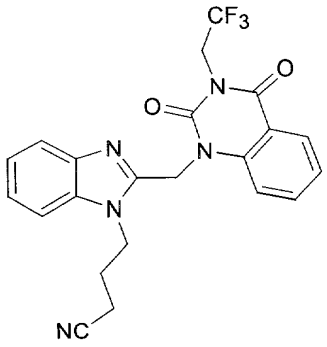
^1H NMR (DMSO-d_6) δ 4.72 (q, J = 9.2 Hz, 2H), 7.20-7.26 (m, 2H), 7.08 (t, J = 7.6 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H);

IR (KBr, cm^{-1}) 1727, 1666, 1163, 1082;

MS m/e 244 (MH^+);

Anal. Calcd for $C_{10}H_7F_3N_2O_2$: C, 49.19; H, 2.89; N, 11.47

Found: C, 49.04; H, 2.85; N, 11.42.



162

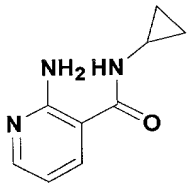
Compound **162** was prepared using the same procedure as compound **160** with compound **162a** and compound **25b**:

^{1}H NMR (DMSO-d_6) δ 2.16-2.18 (m, 2 H), 2.69 (t, J = 7.4 Hz, 2 H), 4.44 (t, J = 7.5 Hz, 2 H), 4.81-4.87 (m, 2 H), 5.71 (s, 2 H), 7.14 (t, J = 7.2 Hz, 1 H), 7.26 (t, J = 7.5 Hz, 1 H), 7.37 (t, J = 7.7 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 1 H), 7.59-7.64 (m, 2 H), 7.78 (t, J = 9.0 Hz, 1 H), 8.15 (d, J = 7.5 Hz, 1 H);

MS m/e 441 (MH^+);

Anal. Calcd for $C_{22}H_{18}F_3N_5O_2 \bullet 0.4\,H_2O$: C, 58.93; H, 4.22; N, 15.62

Found: C, 59.21; H, 4.45; N, 15.41.

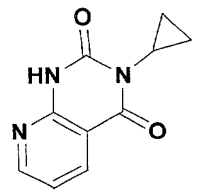


163a

To a solution of 2-aminonicotinic acid (5.0 g, 36.2 mmol), cyclopropylamine (2.0 g, 36.2 mmol), HOBT (4.9 g, 36.2 mmol) in DMF (50 ml) was added EDC (6.9 g, 36.2 mmol) and the mixture stirred for 12h at 23°C. The solvent was removed and the residue dissolved in EtOAc/H_2O. The organic layer is washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to give 3.2 g (50%) of product as a white solid.

^{1}H NMR (DMSO-d6) δ: 0.54-0.59 (m, 2H), 0.66-0.69 (m, 2H), 2.77-2.88 (m, 1H), 3.10-3.40 (br s, 1H), 6.53-6.56 (m, 1H), 7.04 (s, 2H), 7.82 (d, J = 6.2 Hz, 1H), 8.04-8.08 (m, 1H), 8.36-8.42 (m, 1H);

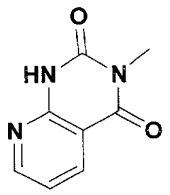
MS m/e 177 (MH^+).



163b

Compound **163b** was prepared as described for **156b** except CDI in CH_2Cl_2 was used in place of ethylchloroformate.

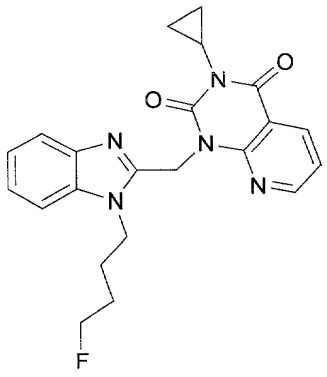
^{1}H NMR (DMSO-d6) δ: 0.71-0.77 (m, 2H), 0.99-1.02 (m, 2H), 2.20-2.25 (m, 1H), 7.22-7.24 (m, 2H), 8.25 (dd, J = 1.5, 7.7 Hz, 1H), 8.56-8.58 (m, 1H);
MS m/e 203 (MH^-).



163c

Compound **163c** was prepared as described for **163b** except CDI in CH_2Cl_2 was used in place of ethylchloroformate.

^{1}H NMR (DMSO-d6) δ: 3.25 (s, 3H), 7.25-7.28 (m, 1H), 8.29 (d, J = 7.8 Hz, 1H), 8.60-8.62 (m, 1H);
MS m/e 177 (MH^-).

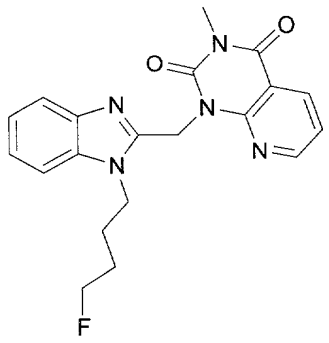


163

3-Cyclopropyl-1-[1-(4-fluoro-butyl)-1H-benzoimidazol-2-ylmethyl]-1H-pyrido[2,3-d]pyrimidine-2,4-dione, **163**, was prepared as described for compound using **163b** and **159c** with BTPP.

^{1}H NMR (DMSO-d6) δ: 0.75-0.79 (m, 2H), 1.04-1.08 (m, 2H), 1.75-1.84 (m, 2H), 1.91-1.96 (m, 2H), 2.76-2.79 (m, 1H), 4.42-4.48 (m, 2H), 4.53 (dt, J = J = 9.7, 41.5 Hz, 2H), 7.11 (t, J = 7.7 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 7.32-7.35 (m,

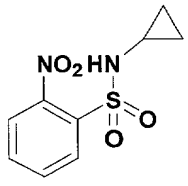
1H), 7.44 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 8.42 (dt, J = 1.7, 7.7 Hz, 1H), 8.58-8.59 (m, 1H);
MS m/e 407 (MH^+).



163d

3-Methyl-1-[1-(4-fluoro-butyl)-1H-benzoimidazol-2-ylmethyl]-1H-pyrido[2,3-d]pyrimidine-2,4-dione, **163d**, was prepared as described for compound using 3-methyl-1H-pyrido[2,3-d]pyrimidine-2,4-dione **163c** and **159c** with BTPP.

^{1}H NMR (DMSO-d6) δ: 1.75-1.83 (m, 2H), 1.93-1.97 (m, 2H), 3.37 (s, 3H), 4.43-4.49 (m, 3H), 4.57 (t, J = 5.9 Hz, 1H), 5.74 (s, 2H), 7.10 (t, J = 7.5 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.36-7.44 (m, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 8.47 (d, J = 7.8 Hz, 1H), 8.62 (d, J = 4.8 Hz, 1H);
MS m/e 381 (MH^+).



164a

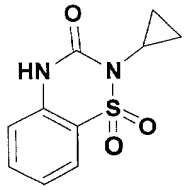
To a -78°C mixture of cyclopropylamine (10 g, 1.75 mmol) in CH_2Cl_2 (100 mL) was added a solution of 2-nitrobenzene sulfonyl chloride (22.1 g, 85.7 mmol) and the mixture was stirred for 12 h. The mixture was washed with 1N HCl dried over $MgSO_4$ then concentrated to give 18.7 g, (88%) of a N-Cyclopropyl-2-nitro-benzenesulfonamide as a tan solid.

^{1}H NMR($CDCl_3$) δ: 0.66-0.70 (m, 2H), 0.70-0.75 (m, 2H), 2.32-2.37 (m, 1H), 5.58 (s, 1H), 7.13-7.78 (m, 2H), 7.83-7.87 (m, 1H), 8.18-8.22 (m, 3H);
MS m/e 242 (MH^+).

164b

A solution of N-cyclopropyl-2-nitro-benzenesulfonamide (7.9 g, 33.0 mmol) in EtOH (50 ml) was treated with HCl (3.0 ml, 4.0 N in dioxane), Pd/C (10%, 100 mg) and shaken in a Parr Hydrogenator at 50 psi for 48 h. The catalyst was removed by filtration and the solvent evaporated to give 6.9 g (84%) of 2-Amino-N-cyclopropyl-benzenesulfonamide as a light grey solid.

^{1}H NMR (DMSO-d6) δ: 0.35-0.37 (m, 2H), 0.42-0.44 (m, 2H), 2.0-2.08 (m, 1H), 5.89 (s, 2H), 6.62 (t, J = 7.1 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 7.27 (t, J = 7.1 Hz, 1H), 7.50 (d, j = 8.0, 1H), 7.82 (s, 1H);
MS m/e 242 (MH^+).

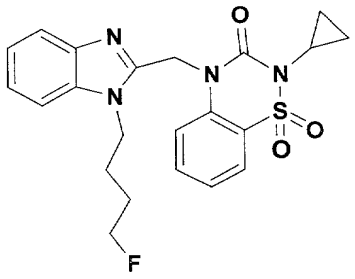


164c

A solution of of 2-amino-N-cyclopropyl-benzenesulfonamide (6.9 g, 32.5 mmol) in CH_2Cl_2 (50 ml) was treated with CDI (6.5 g, 40 mmol) and stirred for 12 h at reflux. The solution was a washed with HCl (1N), dried over $MgSO_4$ and concentrated to give 6.5 g (84%) of 2-cyclopropyl-1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,2,4]thiadiazin-3-one as a brown solid.

^{1}H NMR (DMSO-d6) δ: 0.72-0.80 (m, 2H), 0.90-1.1 (m, 2H), 2.71-2.75 (m, 1H),7.23 (d. 8.1 Hz, 1H), 7.29 (t, J = 7.7 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H);

MS m/e 238 (MH^+).

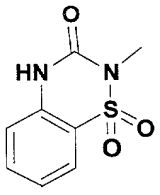


164

2-Cyclopropyl-4-[1-(4-fluoro-butyl)-1H-benzoimidazol-2-ylmethyl]-1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,2,4]thiadiazin-3-one as described for compound **25** using **159c** and **164c**.

^{1}H NMR (DMSO-d6) δ: 0.90-0.96 (m, 2H), 1.06-1.10 (m, 2H), 1.80-1.91 (m, 2H), 2.07-2.13 (m, 2H), 2.91-2.93 (m, 1H), 4.43 (t, J = 8.0 Hz, 2H), 4.54 (dd, J = 5.5, 47.1 Hz, 2H), 6.03 (s, 2H), 7.26 (s, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.52-7.54 (m, 2H), 7.69 (t , J = 7.8 Hz, 1H), 7.80 (d, J = 8.6 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.91-7.93 (m, 1H);

MS m/e 443 (M+).

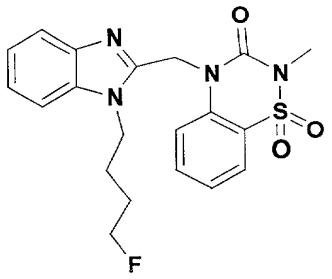


165a

2-Methyl-1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,2,4]thiadiazin-3-one was prepared as described above for compound **164c** except phosgene was used in place of CDI for the ring closure reaction.

^{1}H NMR (DMSO-d6) δ: 3.34 (s, 3H), 7.27-7.34 (m, 2H), 7.71 (t, J = 7.0 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H);

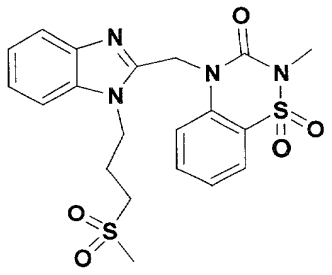
MS m/e 212 (MH^+).



165

Prepared from **165a** and **159c** as described for compound **25**.

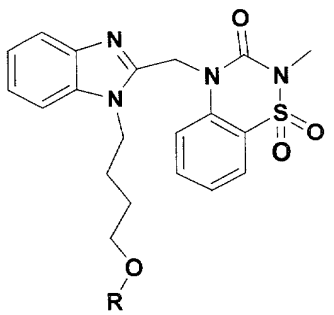
^{1}H NMR (DMSO-d6) δ: 1.74-1.82 (m, 2H), 1.88-1.93 (m, 2H), 3.24 (s, 3H), 4.38 (t, J = 7.3 Hz, 2H), 4.51 (dt, J = 5.9, 47.4 Hz, 2H), 5.57 (s, 2H), 7.15 (t, J = 7.5 Hz, 1H), 7.24 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.8 hz, 1H), 7.51 (d, J= 7.9 hz, 1H), 7.44-7.47 (m, 2H), 7.78 (t, J = 8.1 Hz, 1H), 7.99 (d, J = 7.5 Hz, 1H);
MS m/e 416 (MH^+).



166

A mixture of 2-methyl-1,1-dioxo-1,4-dihydro-2H-1l6-benzo[1,2,4]thiadiazin-3-one (300 mg, 0.71 mmol) and Cs_2CO_3 (0.69, 2.13 mmol) in DMF (20 mL) was stirred for 30 minutes and then treated with **10d** (0.23 g, 0.71 mmol) and stirred for 12 h. The mixture is filtered and concentrated. The residue was purified by preparative thin layer chromatography using 50% EtOAc in hexanes as eluant to give 48 mg (15%) of the product **166** as a clear glass.

^{1}H NMR (DMSO-d6) d: 2.10-2.35 (m, 2H), 2.73 (s, 3H), 2.89 (s, 3H), 3.31-3.39 (m, 2H), 4.40-4.54 (m, 2H), 5.58 (s, 2H);
MS m/e 462 (MH^+).



167, R = H
168, R = Ac

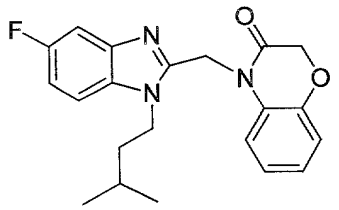
2-methyl-1,1-dioxo-1,4-dihydro-2H-1l6-benzo[1,2,4]thiadiazin-3-one (300 mg, 0.71 mmol) and Cs_2CO_3 (0.69, 2.13 mmol) in DMF (20 mL) was stirred for 30 minutes and then treated **139a** (224 mg, 0.71 mmol) and stirred for 12 h. The mixture was filtered and concentrated. The residue was purified by preparative TLC using 30% EtOAc/hexanes as eluant to give **168,** 48 mg (15%) of the acetate and **167**, 70 mg (24%) of the alcohol. The alcohol could be obtained exclusively by treating the crude reaction mixture with HCl (1N, 10 ml) in MeOH and heating the mixture to reflux for 2 h. Preparative TLC of this reaction gave 147 mg (50%) of **167**.

168, R = Ac

^{1}H NMR (DMSO-d6) δ:1.66-1.74 (m, 2H), 1.85-1.89 (m, 2H), 2.00 (s, 3H), 3.24 (s, 3H), 4.07 (t, J = 6.5 Hz, 2H), 4.37 (t, J = 7.2 Hz, 2H), 5.57 (s, 2H), 7.15 (d, J = 7.9 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.60 (t, J = 7.2 Hz, 1H), 7.78 (t, J = 7.3 Hz, 2H), 7.99 (d, J = 7.9 Hz, 1H); MS m/e 456 (MH^+).

167, R = H:

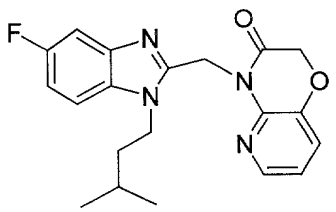
^{1}H NMR (DMSO-d6) d: 1.52-1.55 (m, 2H), 1.81-1.89 (m, 2H), 3.24 (s, 3H), 3.41-3.52 (m, 2H), 4.35 (t, J = 7.5 Hz, 2H), 4.50 (t, J = 5.1 Hz, 1H), 5.57 (s, 2H), 7.14 (t, J = 8.0 Hz, 1H), 7.23 (t, J = 7.2 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.55-7.61 (m, 2H), 7.77 (t, J = 7.2 Hz, 1H), 7.99 (d, J = 6.6 Hz, 1H); MS m/e 456 (MH^+).



169

Compound **169** was prepared using the same procedure as compound **160** with 2H-1,4-benzoxazin-3(4*H*)-one and compound **42d**:

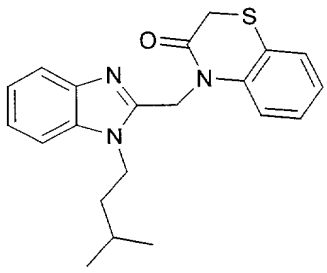
^{1}H NMR (CD_3OD) δ 1.04 (d, J = 6.2 Hz, 6H), 1.76-1.78 (m, 3H), 4.45-4.48 (m, 2H), 4.78 (s, 2H), 5.63 (s, 2H), 7.03-7.09 (m, 3H), 7.14-7.16 (m, 1H), 7.32 (dt, J = 2.4, 9.2 Hz, 1H), 7.39 (dd, J = 2.4, 8.5 Hz, 1H), 7.75 (dd, J = 4.2, 9.1 Hz, 1H); MS m/e 368 (MH^+).



170

Compound **170** was prepared using the same procedure as compound **160** with 2H-pyrido[3,2-B]-1,4-oxazin-3(4*H*)-one and compound **42d**:

^{1}H NMR (CD_3OD) δ 1.06 (d, J = 6.4 Hz, 6 H), 1.80-1.88 (m, 3 H), 4.56-4.60 (m, 2 H), 4.90 (s, 2 H), 5.76 (s, 2 H), 7.08 (dd, J = 4.9, 8.0 Hz, 1 H), 7.34-7.43 (m, 3 H), 7.82 (dd, J = 4.3, 9.1 Hz, 1 H), 7.92 (dd, J = 1.3, 4.9 Hz, 1 H); MS m/e 369 (MH^+).



171

A solution of the compound **4b** (0.5 g, 2.29 mmol) and 2H-1,4-benzothiazin-3(4*H*)-one (0.38 g, 2.29 mmol) containing tributylphosphine (0.61 g, 3.0 mmol) in benzene (5 ml) was treated with 1,1'-(azodicarbonyl)dipiperidine (0.76 g, 3.0 mmol). The mixture was stirred at room temperature for 12 hours. The solvent was removed. The residue was purified by flash chromatography (15% EtOAc in hexanes) and further purified by preparative HPLC (C18, gradient 30% MeOH/Water to 90% MeOH/water with 0.1% TFA) to give 150 mg (20% yield) of compound **171** as a white solid:

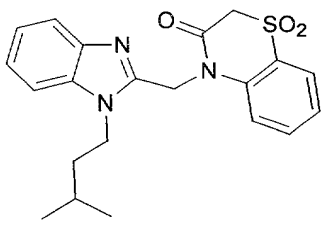
^{1}H NMR (DMSO-d_6) δ 0.97 (d, J = 6.2 Hz, 6 H), 1.6-1.8 (m, 3 H), 3.33 (s, 2 H), 3.61 (s, 2 H), 3.41-4.13 (m, 2 H), 5.43 (s, 2 H), 7.01 (t, J = 7.5 Hz, 1 H), 7.14-7.27 (m, 3 H), 7.41 (t, J = 7.5, 2 H), 7.52 (t, J = 7.9 Hz, 2 H);

IR (KBr, cm^{-1}) 2955, 1673, 1479, 1449, 1384, 741;

MS m/e 365 (MH^+);

Anal. Calcd for $C_{21}H_{23}N_3OS$: C, 69.01; H, 6.34; N, 11.50

Found: C, 68.84; H, 6.31; N, 11.45.



172

A solution of compound **171** (300 mg, 0.8 mmol) and 3-chloroperbenzoic acid (80%, 350 mg, 1.64 mmol) in CH_2Cl_2 (20 ml) was stirred at room temperature for 12 hours. The reaction mixture was washed with saturated aqueous $NaHSO_3$ and saturated aqueous $NaHCO_3$ then dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 3:2) to give 60 mg (18% yield) of compound **172** as a white solid:

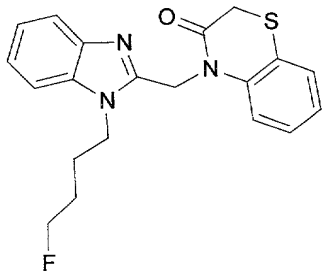
^{1}H NMR (DMSO-d_6) δ 0.98 (d, J = 6.1 Hz, 6 H), 1.60-1.73 (m, 3 H), 4.26-4.34 (m, 2 H), 5.00 (s, 2 H), 5.52 (s, 2 H), 7.13-7.27 (m, 2 H), 7.41 (t, J = 7.0 Hz, 1 H), 7.54 (t, J = 8.1 Hz, 2 H), 7.73-7.79 (m, 2 H), 7.91 (d, J = 7.7 Hz, 1 H);

IR (KBr, cm^{-1}) 2954, 1692, 1482, 1319, 1171, 738;

MS m/e 397 (MH^+);

Anal. Calcd for $C_{21}H_{23}N_3O_3S$: C, 63.46; H, 5.83; N, 10.57

Found: C, 63.17; H, 5.86; N, 10.30.

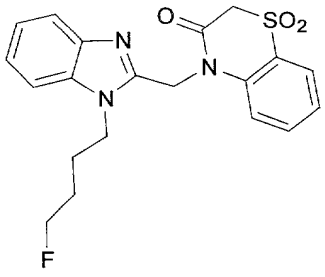


173

Compound 173 was prepared as described for compound **25** with **159c** and 2H-1,4-benzothiazin-3(4H)-one using BTPP.

^1H NMR (DMSO-d6) δ: 1.77-1.85 (m, 2H), 1.92-1.97 (m, 2H), 3.50 (s, 2H), 4.30 (t, J = 7.6 Hz, 1H), 4.49 (dt, J = 5.8, 47.1 Hz, 2H), 5.52 (s, 2H), 7.00 (t, J = 8.0 Hz, 1H), 7.22-7.28 (m, 5H), 7.32-7.34 (m, 1H), 7.72 (t, J = 7.9 Hz, 1H);

MW m/e 369 (MH^+).

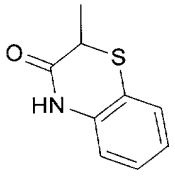


174

To a solution of sulfide (200 mg, 0.54 mmol) in DMF (20 ml) was treated wth MPP (560 mg, 1.14 mmol) and stirred for 12 h. The solvent was removed and the residue was dissolved in EtOAc/H_2O. The organic layer was washed with saturated $NaHCO_3$, then dried over $MgSO_4$ and concentrated to give 60 mg

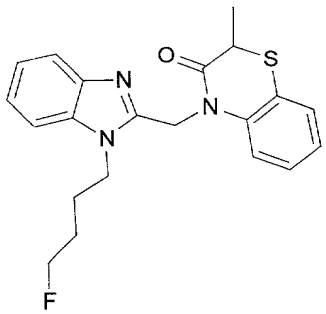
(30%), of 4-[1-(4-fluoro-butyl)-1H-benzoimidazol-2-ylmethyl]-1,1-dioxo-1,4-dihydro-2H-1λ⁶-benzo[1,4]thiazin-3-one.

^{1}H NMR (DMSO-d6) δ: 1.73-1.81 (m, 2H), 1.86-1.92 (m, 2H), 4.38 (t, J = 5.8 Hz, 2H), 4.50 (dt, J = 6.0 , 47.3 Hz, 2H), 4.99 (s, 2H), 5.53 (s, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.25 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.7 (t, J = 8.1 Hz, 1H), 7.91 (d, J = 7.7 Hz, 1H);
MS m/e 401 (MH^+).



175a

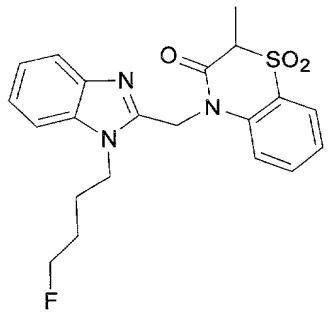
To a mixture of 2-bromopropionic acid (1.21 g, 8.0 mmol), 2-aminothiophenol (1.0 g, 8.0 mmol), HOBT (1.1g, 8.0 mmol) in DMF (50 ml) was added EDC (1.53 g, 8.0 mmol) and the mixture stirred for 12 h then concentrated. The residue was dissolved in EtOAc/H_2O. The organic layer was washed with saturated $NaHCO_3$, dried over MgSO4 and concetrated. The residue solidified on standing to give the product 0.72 g, (50%) as a tan solid.
^{1}H NMR (DMSO-d6) δ: 1.32 (d, J = 11.7Hz, 3H), 3.65 (q, J = 7.0 Hz, 1H), 6.96-6.99 (m, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H);
MS m/e 178 (MH^+).



175

Compound **175** was prepared as described for compound **25** using compound **175a** and **159c** with BTPP instead of Cs_2CO_3.

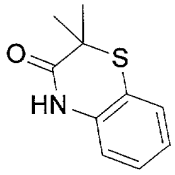
^{1}H NMR (DMSO-d6) δ: 1.37 (d, J = 6.9 Hz, 1H), 1.71-1.80 (m, 2H), 1.83-1.87 (m, 2H), 3.76 (q, J = 6.8 Hz, 1H), 4.33-4.37 (m, 2H), 4.49 (dt, J = 6.0, 47 Hz, 2H), 5.35 (d, J = 16.8,Hz, 1H), 5.49 (d, J = 16.8 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 7.16 (t, J = 7.2 Hz, 1H), 7.21-7.28 (m, 2H), 7.42 (t, J = 6.4 Hz, 2H), 7.54 (d, J = 8.0 hz, 1H), 7.58 (d, j = 8.0 Hz, 1H);
MS m/e 383 (MH^+).



176

To a solution of sulfide (1.64 g, 0.43 mmol) in DMF (20 ml) was treated wth MPP (4.45 mg, 0.90 mmol) and stirred for 12 h. The solvent was removed and the residue was dissolved in EtOAc/H_2O. The organic layer was washed with saturated $NaHCO_3$, then dried over $MgSO_4$ and concentrated. The yellow oil was purified by preparative TLC to give **176** 60 mg (30%), as a yellow oil.

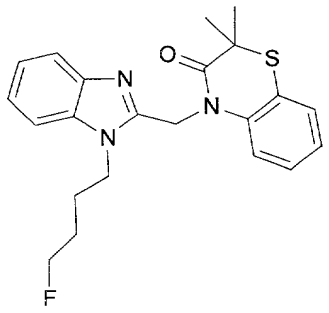
^{1}H NMR (DMSO-d6) δ: 1.48 (d, J = 6.9 Hz, 3H), 1.65-1.79 (m, 2H), 1.80-1.95 (m, 2H), 4.30-4.45 (m, 2H), 4.50 (dt, J = 5.9, 47 Hz, 2H), 5.03 (q, J = 6.9 Hz, 1H), 5.40 (d, j = 17 Hz, 1H), 5.64 (d, J = 17 Hz, 1H), 7.17 (t, 7.6 Hz, 1H), 7.25 (t, j = 8.0 Hz, 1H), 7.45 (t, J = 7.3 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.60 (d, j = 8.0 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.78 (t, J = 8.2 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H);
MS m/e 415 (MH^+).



177a

To a slurry of NaH (0.64 g, 16 mmol) in DMF (20 ml) was added 2-aminothiophenol (2.0 g, 16 mmol) and the mixture stirred until gas evolution ceased. 2-methyl-2-bromopropionic acid ethyl ester (3.12 g, 2.34 ml, 16 mmol) and the mixture stirred for 8 h. The solvent was removed and the residue dissolved in toluene and heated to reflux for 12 h. The solvent was removed to give **177a** 2.87 g (92 %) as a tan solid.

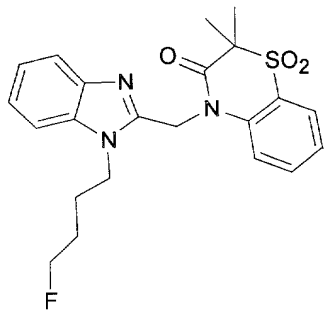
^{1}H NMR (DMSO-d6) δ: 1.49 (s, 6H), 6.88 (d, J = 8 Hz, 1H), 7.01 (t, J = 7.5 hz, 1H), 7.17 (t, J = 6.7 z, 1H), 7.26-7.29 (m, 1H), .72 (br s, 1H);
MS m/e 193 (MH^+).



177

Compound **177** was prepared as described for compound **25** using **159c** and **177a** with BTPP instead of Cs_2CO_3.

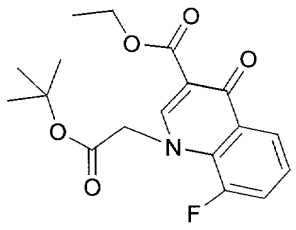
^{1}H NMR (DMSO-d6) δ: 1.39 (s, 6H), 1.73-1.79 (m, 2H), 1.85-1.88 (m, 2H), 4.35 (t, J = 7.1 Hz, 2H), 4.50 (dt, J = 5.7, 47.3 Hz, 2H), 5.43 (s, 2H), 7.08 (t, J = 7.5 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H), 7.22 (t, J = 7.2 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 8.9 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H);
MS m/e 397 (MH^+).



178

4-[1-(4-Fluoro-butyl)-1H-benzoimidazol-2-ylmethyl]-2,2-dimethyl-1,1-dioxo-1,4-dihydro-2H-1λ⁶-benzo[1,4]thiazin-3-one was prepared as described for compound **176** above.

^{1}H NMR (DMSO-d6) δ: 1.50 (s, 6H),1.75-1.80 (m, 2H), 1.89-1.92 (m, 2H), 4.37 (t, J = 7.3 Hz, 1H), 4.51 (dt, J = 5.9 , 47.4 Hz, 2H), 5.52 (s, 2H), 7.15 (t, J = 7.9 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.95 (d, J = 7.7 Hz, 1H);
MS m/e 429 (MH^+).



179a

To a slurry of sodium hydride (0.44g, 8.50 mmol) in DMF (50 mL) was added ethyl 1,4-dihydro-8-fluoro-4-oxoquinoline-3-carboxylate [Maybridge](2.0 g, 8.50 mmole) and the mixture was stirred until gas evolution ceased. *T*-butyl bromoacetate (1.75 g, 9.00 mmol) was added and the mixture was stirred for 12 hours at room temperature. The solvent was removed. The residue was dissolved in EtOAc and washed with water. The organic extracts were dried with $MgSO_4$

and evaporated. The residue was purified by flash chromatography (3% MeOH/CH_2Cl_2) to give 2.35 g (79% yield) of compound **179a** as a white solid:

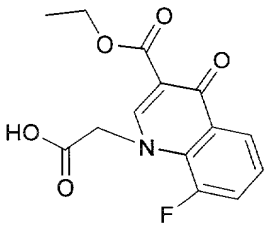
^{1}H NMR (DMSO-d_6) δ 1.29 (t, J = 6.9 Hz, 3 H), 1.43 (s, 3 H), 4.24 (q, J = 6.9 Hz, 2 H), 5.21 (d, J = 7.5 Hz, 2 H), 7.44-7.49 (m, 1 H), 7.65 (dd, J = 7.8, 16.0 Hz, 1 H), 8.10 (d, J = 7.2 Hz, 1 H), 8.65 (s, 1 H);

IR (KBr, cm^{-1}) 1739, 1722, 1243;

MS m/e 349 (MH^+);

Anal. Calcd for $C_{18}H_{20}FNO_5$: C, 61.88; H, 5.77; N, 4.01

Found: C, 61.73; H, 5.69; N, 4.08.



179b

Compound **179a** (2.0 g, 5.70 mmol) was stirred with TFA (20 mL) for 12 hours then concentrated to give an oil. The oil was triturated with water and filtered to give 1.6 g (99% yield) of compound **179b** as a tan solid:

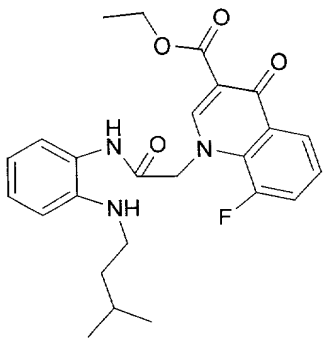
^{1}H NMR (DMSO-d_6) δ 1.29 (t, J = 7.1 Hz, 3 H), 4.25 (d, J = 7.1 Hz, 2 H), 5.24 (d, J = 4.4 Hz, 2 H), 7.44-7.48 (m, 1 H), 7.47 (dd, J = 7.9, 16 Hz, 1 H), 8.09 (d, J = 7.9 Hz, 1 H), 8.66 (s, 1 H);

IR (KBr, cm^{-1}) 1728, 1688;

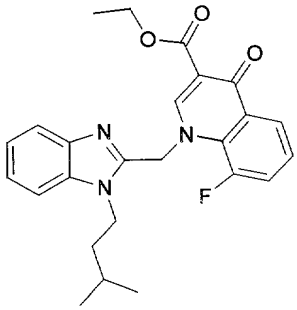
MS m/e 293 (MH^+);

Anal. Calcd for $C_{14}H_{12}FNO_5$: C, 56.43; H, 4.20; N, 4.73

Found: C, 56.43; H, 4.15; N, 4.75.



179c



179

To a mixture of compound **179b** (1.5g, 1.70 mmol) and 2-chloro-1-methyl pyridinium iodide (0.522, 2.04 mmol) in CH_3CN (50 ml) was added triethylamine (0.48 ml, 1.70 mmol) followed by compound **157b** (0.3 g, 1.70 mmol). The mixture was stirred for 12 hours at room temperature. The reaction mixture was filtered to give 0.44 g (57%) of the intermediate **179c** as a white solid. The solid (0.44 g, 0.97 mmol) was dissolved in AcOH (25 ml) and heated to reflux for 4 hours then cooled and concentrated. The residue was purified by flash chromatography (3% MeOH in CH_2Cl_2) to give 289 mg (69% yield) of compound **179** as a white solid:

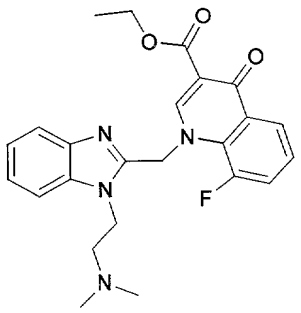
^{1}H NMR (DMSO-d_6) δ 1.02 (d, J = 5.7 Hz, 6 H), 1.29 (t, J = 6.9 Hz, 3 H), 1.68-1.72 (m, 3 H), 4.22-4.31 (m, 4 H), 6.09 (d, J = 4.5 Hz, 2 H), 7.12 (t, J = 7.5 Hz, 1 H), 7.24 (t, J = 7.5 Hz, 1 H);

IR (KBr, cm^{-1}) 2958, 1718, 1610, 1561, 1260, 1129;

MS m/e 435 (MH^+);

Anal. Calcd for $C_{25}H_{26}FN_3O_3 \bullet 0.64\ H_2O$: C, 67.17; H, 6.15; N, 9.40

Found: C, 67.17; H, 6.14; N, 9.12.



180

Compound **180** was prepared as a tan foam using the same procedure as compound **179** with compound **179b** and compound **98b** in 51% yield:

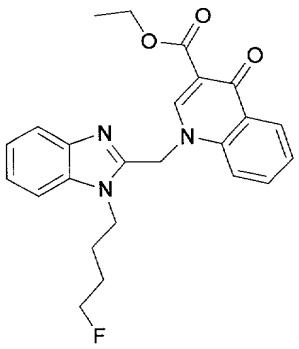
^{1}H NMR (DMSO-d_6) δ1.29 (t, J = 7.2 Hz, 3 H), 2.27 (s, 6 H), 2.66 (t, J = 6.3 Hz, 2 H), 4.25 (q, J = 7.2 Hz, 2 H), 4.38 (t, J = 6.3 Hz, 2 H), 6.09 (s, 2 H), 7.09 (t, J = 7.2 Hz, 1 H), 7.15 (t, J = 7.2 Hz, 1 H), 7.40-7.52 (m, 4 H), 8.13 (d, J = 9 Hz, 1 H), 8.78 (s, 1 H);

IR (KBr, cm^{-1}) 1725, 1695;

MS m/e 436 (MH^+);

Anal. Calcd for $C_{24}H_{25}FN_4O_3 \bullet 0.72\ H_2O$: C, 64.16; H, 5.93; N, 12.47

Found: C, 64.15; H, 5.84; N, 12.11.

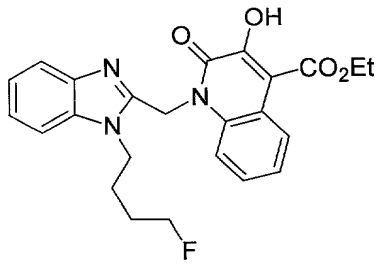


181

Compound **181** was prepared as described for compound **25** using **159c** and 4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (prepared as described by

Gould, R. G.; Jacobs, W. A.; *J. Am. Chem. Soc.* **1939**, *61*, 2890) using BTPP as described for compound **25.**

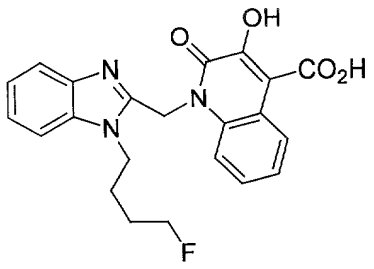
^{1}H NMR (DMSO-d6) δ: 1.29 (t, J = 7.1 Hz, 2H), 1.70-1.84 (m, 4H), 4.25 (q, J = 7.1 hz, 1H), 4.42-4.48 (m, 3H), 4.56 (dt, J = J, 5.9, 47 Hz, 1H), 6.06 (s, 2H), 7.15 (t, J = 7.3 Hz, 1H), 7.24 (t, J = 7.3 Hz, 1H), 7.44-7.49 (m, 2H), 7.62-7.66 (m, 3H), 8.26 (d, J = 7.9 Hz, 1H), 8.93 (s, 1H);
MS m/e 421 (MH^+).



182

A solution containing the isatin **114a** (215 mg, 0.61 mmol), diethyl amine (63 μL, 0.61 mmol) and ethyl diazoacetate (128 μL, 1.22 mmol) in DMF-EtOH (1:1, 6 mL) was stirred at room temperature for 15 hours. The solvents were removed *in vacuo* and to the residue was added 1M HCl (10 mL). After stirring for 30 min. the mixture was extracted with ethyl acetate (2x15 mL). The aqueous phase was neutralized with solid $NaHCO_3$ and extracted with ethyl acetate (2x 15 mL). The organic phases were combined and washed with brine (10 mL), and dried ($MgSO_4$) to give **182** (294 mg, 100%) as a yellow solid.

^{1}H NMR ($CDCl_3$) δ 8.85 (br s, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 7.7 Hz, 1H), 7.79 (m, 1H), 7.46 (t, J = 7.3 Hz, 1H), 7.32 (m, 4H), 6.04 (s, 2H), 4.55 (q, J = 7.1 Hz, 2H), 4.40 (dt, J = 5.6, 47 Hz, 2H), 4.31 (t, J = 7.6 Hz, 2H), 1.68 (m, 4H), 1.47 (t, J = 7.1 Hz, 3H);
MS m/e 438 (MH^+).

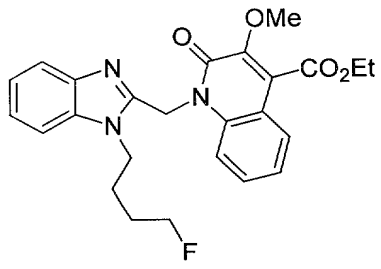


183

A mixture of the ethyl ester **182** (294 mg, 0.672 mmol) in water (5 mL), 1M NaOH (3.4 mL), dioxane (4mL) was heated at reflux temperature for 3 hours. 1M NaOH (5 mL) was added and heating was continued for 1 hour. The mixture was cooled to room temperature and acidified to pH 3 with 1 M HCl. Extraction with ethyl acetate (4x 20 mL) and washing with brine (10 mL), drying ($MgSO_4$) afforded the pure **183,** 150 mg (55%) as a white solid.

^{1}H NMR (DMSO) δ 7.61 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 7.23 (m, 2H), 7.14 (t, J 7.5 Hz, 1H), 5.88 (s, 2H), 4.50 (m, 4H), 1.80 (m, 4H);

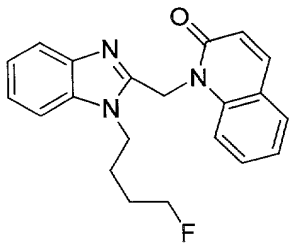
MS m/e 410 (MH^+).



184

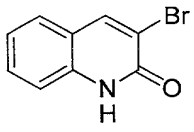
To a solution of the quinolone **182**(52 mg, 0.12 mmol) in DMF (2 mL) was added Cs_2CO_3 (82 mg, 0.25 mmol). After stirring for 5 min. MeI (9.0 µL, 0.14 mmol) was added and stirring was continued for 4 hours. The volatiles were removed *in vacuo* and the residue suspended in water. The product was extracted into ethyl acetate (2x 12 mL), the combined organic fractions washed with brine (5 mL) and dried ($MgSO_4$). Purification by flash column chromatography (eluent 2% methanol in methylene chloride) gave 21 mg (39%) of **184** as a white solid.

^{1}H NMR ($CDCl_3$) δ 8.17 (d, J = 8.6 Hz, 1H), 7.76 (m, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.27 (m, 4H), 5.92 (s, 2H), 4.51 (q, J = 7.2 Hz, 2H), 4.40 (m, 4H), 4.06 (s, 3H), 1.67 (m, 4H), 1.44 (t, J = 7.2 Hz, 3H);
MS m/e 452 (MH^+).



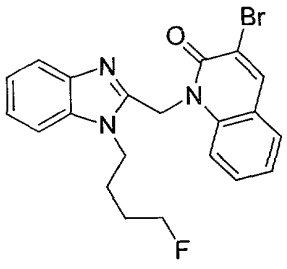
185

Compound **185** was prepared as described for compound **25** from 2-hydroxyquinoline (52 mg, 0.36 mmol) and compound **159c**. Compound **185** was obtained after purification by flash column chromatography (eluent 2% methanol in methylene chloride) to give 60 mg (48%) of **185** as an off-white solid.
^{1}H NMR (DMSO) δ 8.02 (d, J = 9.5 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.62 (d, J = 8.6 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.55 (t, J 8.2 Hz, 1H), 7.47 (d, J 8.0 Hz, 1H), 7.27 (d, J = 7.3 Hz, 1H), 7.22 (t, J = 7.3 Hz, 1H), 7.13 (t, J = 7.3 Hz, 1H), 6.70 (d, J = 9.5 Hz, 1H), 5.80 (s, 2H), 4.49 (m, 4H), 1.80 (m, 4H);
MS m/e 350 (MH^+).



186a

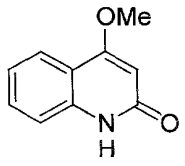
Compound **186a** was prepared according to the procedure reported by Sabol *et al.*, *Synth. Commun.*, **2000**, *30*, 427-432.



186

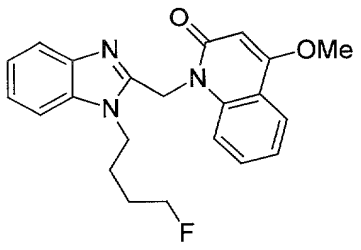
Compound **186** was prepared as described for the preparation of compound **25** using **186a** (538 mg, 2.40 mmol) and **159c**. The crude product **186** was obtained after precipitation from water. Recystallization from ethyl acetate afforded 463 mg (45%) of **186** as an off-white solid.

^{1}H NMR (DMSO) δ 8.67 (s, 1 H), 7.80 (d, J = 7.8 Hz, 1H), 7.62 (m,3H), 7.45 (d, J = 8.0 Hz, 1H), 7.32 (t, J = 7.8 Hz, 1H), 7.23 (t, J 8.0 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 5.86 (s, 2H), 4.51 (m, 4H), 1.82 (m, 4H);
MS m/e 428 (M^+).



187a

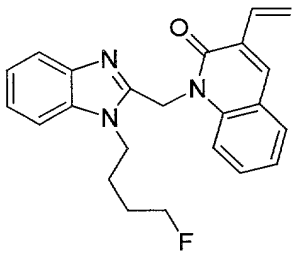
To a suspension of 2,4-dihydroxy quinoline (3.00 g, 18.6 mmol) and potassium carbonate (5.14 g, 37.2 mmol) in acetone (500 mL) was added dimethyl sulfate (2.1 mL, 22 mmol) and the resulting mixture heated at reflux during 5 hrs. The solvent was removed *in vacuo* and the residue triturated in water. The product was collected by filtration, washed with water and triturated from methanol to give 4-methoxy 2-quinolone **187a** (1.76 g, 54%) as a white solid, that had identical ^{1}H NMR data as reported (Reisch *et al.*, *Arch. Pharm.*, **1980**, *313*, 751-755).



187

Compound **187** was prepared as described for compound **25** using **187a** (529 mg, 3.02 mmol) and **159c**. Compound **187** was purified by flash column chromatography (eluent 2% methanol in methylene chloride) to give 200 mg (17%) of **187** as an off-white solid.

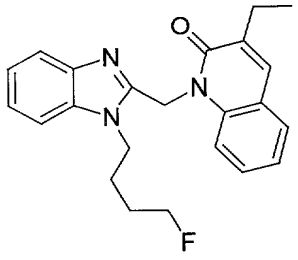
^{1}H NMR (DMSO) δ 7.93 (d, J = 7.5 Hz, 1H), 7.58 (m, 3H), 7.47 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 7.3 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 6.14 (s, 1H), 5.76 (s, 2H), 4.48 (m, 4H), 4.00 (s, 3H), 1.78 (m, 4H); MS m/e 380 (MH^+).



188

A mixture of the bromide **186** (101 mg, 0.236 mmol), $Pd(PPh_3)_4$ (27 mg, 0.024 mmol), vinyl tri-*n*butyltin (83 μL, 0.28 mmol) in toluene (1.2 mL) was heated at reflux for 1.5 hours under a nitrogen atmosphere. The mixture was cooled to room temperature, water and ethyl acetate (15 mL) were added and the layers separated. The organic phase was washed with water (2 x 10 mL), brine and dried with Na_2SO_4. The remaining yellow solid was washed with hexane and diethyl ether to give 100 mg product that was further purified by reverse phase preparative HPLC to give 40 mg (45%) of **188**.

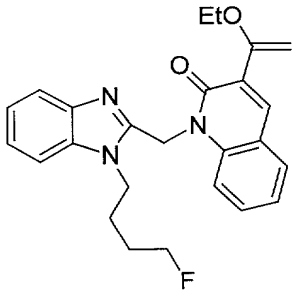
^{1}H NMR (CD_3OD) δ 8.12 (s, 1 H), 7.73 (d, J 7.9 Hz, 1 H), 7.50 (m, 4 H), 7.27 (m, 2 H), 7.18 (t, J 7.5 Hz, 1 H), 6.97 (dd, J 11.3, 17.7 Hz, 1 H), 6.14 (d, J 17.7 Hz, 1 H), 5.89 (s, 2 H), 5.42 (d, J 11.3, 1 H), 4.43 (m, 4 H), 1.80 (m, 4 H);
MS m/e 376 (MH^+).



189

A mixture of the alkene **188** (21 mg, 0,056 mmol) and Pd-C (10%, 3 mg) in THF (1 mL) was stirred under a hydrogen atmosphere for 3 hours. The catalyst was filtered off and the filtrate concentrated to give compound **189** (21 mg, 100%) as a brownish solid.

^{1}H NMR (DMSO) δ 7.86 (s, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.60 (m, 2H), 7.48 (m, 2H), 7.23 (m, 2H), 7.13 (t, J = 7.7 Hz, 1 H), 5.82 (s, 2 H), 4.49 (m, 4H), 2.58 (q, J = 7.4 Hz, 2H), 1.77 (m, 4H), 1.21 (t, J = 7.4 Hz, 3H);
MS m/e 378 (MH^+);



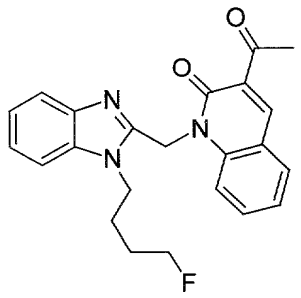
190

A mixture of the bromide **186** (51 mg, 0.119 mmol), $Pd(PPh_3)_4$ (14 mg, 0.012 mmol), ethoxyvinyl tri-*n*-butyltin (48 μL, 0.14 mmol) in toluene (1.2 mL) was heated at reflux for 2.5 hours under a nitrogen atmosphere. The mixture was

cooled to room temperature, water and ethyl acetate (15 mL) were added and the layers separated. The organic phase was washed with water (2 x 10 mL), brine and dried with Na_2SO_4. The remaining yellow solid was triturated from diethyl ether overnight to give compound **190** (34 mg, 68%) product.

^{1}H NMR (DMSO) δ 8.33 (s, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.59 (m, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.30 (m, 2H), 7.22 (t, J = 7.3 Hz, 1H), 7.12 (t, J 7.3 Hz, 1H), 5.85 (s, 2H), 5.71 (s, 1H), 4.61 (s, 1H), 4.50 (m, 4H), 3.91 (q, J = 7.0 Hz, 2H), 1.80 (m, 4H), 1.39 (t, J = 7.0 Hz, 3H);

MS m/e 420 (MH^+);

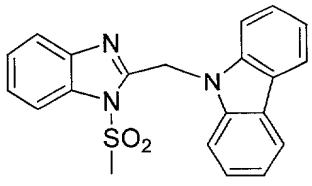


191

A solution of the vinyl ether **190** (12 mg, 0.029 mmol) in 1:1 1M HCl-THF (2 mL) was stirred at room temperature for 1 hour. The solvents were removed and the residue precipitated from diethyl ether to give 8 mg (70%) of **191** as an off-white solid.

^{1}H NMR (DMSO) δ 8.65 (s, 1H), 8.07 (d, J = 7.7 Hz, 1H), 7.74 (t, J = 7.9 Hz, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.60 (m, 2H), 7.40 (m, 2H), 7.25 (t, J = 7.3 Hz, 1H), 6.02 (s, 2H), 5.71 (s, 1H), 4.54 (m, 2 H), 2.61 (s, 3H), 1.89 (m, 4H);

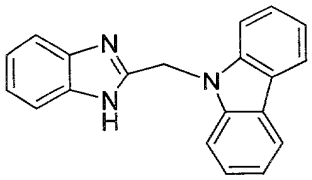
MS m/e 392 (MH^+);



192a

To a suspension of carbazole (226 mg, 1.35 mmol) in CH_3CN (8 mL) was added sodium hydride (60% suspension in mineral oil, 54 mg, 1.35 mmol). This mixture was stirred at room temperature for 30 minutes prior to addition of compound **1b** (500 mg, 1.45 mmol). After 3 hours, the reaction mixture was diluted with water and the orange solid was filtered. The solid was dissolved in CH_2Cl_2 and washed with brine solution. The organic layer was dried over $MgSO_4$ and evaporated. Flash column chromatography (3:1 hexanes/ EtOAc) gave 53 mg (10% yield) of compound **192a** :

^1H NMR ($CDCl_3$) δ 2.58 (s, 3 H), 5.92 (s, 2 H), 7.17-7.21 (m, 4 H), 7.31-7.38 (m, 2 H), 7.51 (d, J = 8.3 Hz, 2 H), 7.72-7.79 (m, 2 H), 8.02 (d, J = 7.7 Hz, 2 H);
IR (KBr, cm^{-1}) 3436, 2918, 1455, 1370, 1210, 1159, 1148, 744, 545;
MS m/e 376 (MH^+);
Anal. Calcd for $C_{21}H_{17}N_3O_2S \bullet 0.25\ H_2O$: C, 66.38; H, 4.64; N, 11.06
Found: C, 66.49; H, 4.64; N, 10.81.

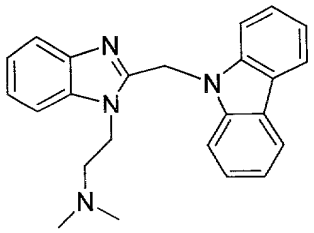


192b

Compound **192a** (166 mg, 0.44 mmol) was dissolved in CH_3OH / CH_2Cl_2 (20 mL, 1:1 ratio). Hydrazine (1.53 g, 47.78 mmol) was added and the reaction mixture was stirred at reflux for 48 hours. The solvent was evaporated to give a white residue which was triturated with water and then filtered to give 117 mg (89% yield) of compound **192b**:

^1H NMR (CD_3OD) δ 5.82 (s, 2 H), 7.16-7.25 (m, 4 H), 7.42 (td, J = 1.2, 7.1 Hz, 3 H), 7.52 (d, J = 8.2 Hz, 3 H), 8.12 (d, J = 7.6 Hz, 2 H);
IR (KBr, cm^{-1}) 3049, 2642, 1625, 1460, 1326, 1210, 1034, 748, 722;
MS m/e 298 (MH^+);
Anal. Calcd for $C_{20}H_{15}N_3 \bullet 0.40\ H_2O$: C, 78.87; H, 5.23; N, 13.80

Found: C, 78.88; H, 5.23; N, 13.44.



192

To compound **192b** (50 mg, 0.17 mmol) suspended in THF (5 mL) was added NaH (60% suspension in mineral oil, 20 mg, 0.50 mmol). After stirring at room temperature for 20 minutes, 2-chloro-N,N-dimethylethylamine hydrochloride (27 mg, 0.19 mmol) was added and the reaction mixture was stirred at 60 °C for 16 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ and was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$ and evaporated. Column chromatography (gradient hexanes/EtOAc, 1:1 to straight EtOAc) gave 29 mg (47% yield) of compound **192**:

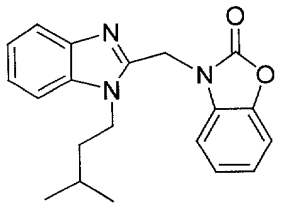
^1H NMR ($CDCl_3$) δ 1.77 (s, 6H), 1.80 (t, J = 7.5 Hz, 2H), 3.97 (t, J = 7.5 Hz, 2H), 5.83 (s, 2H), 7.24-7.31 (m, 5H), 7.41-7.46 (m, 2H), 7.58 (d, J = 8.2 Hz, 2H), 7.85 (d, J = 6.4 Hz, 1H), 8.10 (dd, J = 0.6, 7.2 Hz, 2H);

IR (KBr, cm^{-1}) 3413, 2933, 1597, 1485, 1461, 1323, 1258, 1209, 742, 718;

MS m/e 369 (MH^+);

Anal. Calcd for $C_{24}H_{24}N_4 \bullet 0.70\ H_2O$: C, 75.64; H, 6.72; N, 14.70

Found: C, 75.87; H, 6.64; N, 14.32.



193

Compound **194** was prepared using the same procedure as compound **4** with compound **4c** and 2-benzoxazolinone:

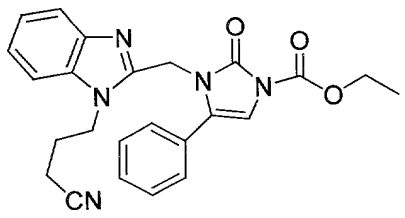
^{1}H NMR ($CDCl_3$) δ 0.98 (d, J = 6.6 Hz, 6H), 1.44-1.52 (m, 2H), 1.68-1.79 (m, 1H), 4.26-4.32 (m, 2H), 5.35 (s, 2H), 7.05-7.22 (m, 3H), 7.29- 7.35 (m, 3H), 7.38-7.41 (m, 1H), 7.79-7.82 (m, 1H);

IR (KBr, cm^{-1}): 2958, 1760, 1486, 1241, 1021, 755, 741;

MS m/e 336 (MH^+);

Anal. Calcd for $C_{20}H_{21}N_3O_2 \bullet 0.25\ H_2O$: C, 70.67; H, 6.38; N, 12.36

Found: C, 70.89; H, 6.41; N, 12.30.



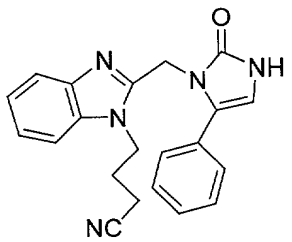
194

Compound **194** was prepared using the same procedure as compound **69** starting with compound **25b** and 3-ethoxycarbonyl-5-phenyl-imidazolone (Meanwell, N.A. et al , *J. Org. Chem*, **1995**, *60*, 1565-82).

.

^{1}H NMR (d_6-DMSO) δ 1.31 (t, J=7.0 Hz, 3H), 1.95-2.00 (m, 2H), 2.51-2.54 (m, 2H), 4.27-4.31 (m, 2H), 4.32-4.36 (m, 2H), 5.09 (s, 2H), 7.03 (d, J=6.8 Hz, 1H), 7.19-7.26 (m, 2H), 7.39-7.42 (m, 3H), 7.54-7.60 (m, 4H);

MS m/e 430 (MH^+).

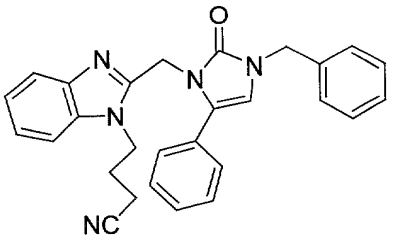


195

To a solution of **194** (62 mg, 0.14 mmol) in THF (1 mL) was added dimethylamine (2M in THF, 0.5 mL, 0.5 mmol) and stirred for 1 h. The product precipitated out the solution was collected by filtration to give 46 mg (89%) of **195** as a white solid.

^{1}H NMR (d_6-DMSO) δ 1.99-2.02 (m, 2H), 2.56 (t, J=7.4 Hz, 2H), 4.32 (t, J=7.4 Hz, 2H), 5.07 (s, 2H), 6.65 (d, J=2.4 Hz, 1H), 7.16-7.19 (m, 1H), 7.22-7.30 (m, 2 H), 7.34 (t, J=7.4 Hz, 2H), 7.50 (d, J=7.2 Hz, 2H), 7.56-7.58 (m, 2H), 10.38 (s, 1H);

MS m/e 358 (MH^+).

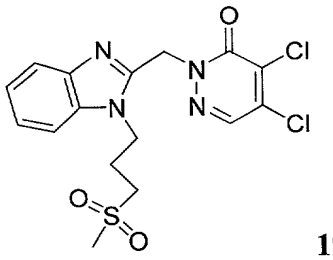


196

Compound **196** was prepared as described for compound **25**.

^{1}H NMR ($CDCl_3$) δ 2.05-2.10 (m, 2H), 2.32 (t, J=7.0 Hz, 2H), 4.39 (t, J=7.2 Hz, 2H), 4.86 (s, 2H), 5.14 (s, 2H), 6.24 (d, J=5.4 Hz, 1H), 7.24-7.47 (m, 13H), 7.71 (d, J=7.5 Hz, 1H);

MS m/e 448 (MH^+).



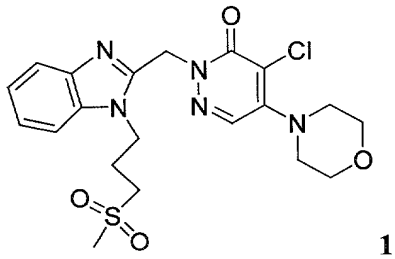
197

Compound **197** was prepared using the same procedure as compound **25** starting with compound **10d** and 4,5-dichloro-3-hydroxypyridazine.

^{1}H NMR ($CDCl_3$) δ 2.45-2.49 (m, 2H), 2.99 (s, 3H), 3.17 (t, J=6.9 Hz, 2H), 4.59 (t, J=7.1 Hz, 2H), 5.66 (s, 2H), 7.25-7.32 (m, 2H), 7.40 (d, J=7.8 Hz, 1H), 7.74 (d, J=7.6 Hz, 1H), 7.92 (s, 1H);

MS m/e 415 (MH^+);

Anal. Calcd for $C_{16}H_{16}Cl_2N_4O_3S$: C, 46.27; H, 3.88; N, 13.49. Found: C, 46.25; H, 3.90; N, 13.49.



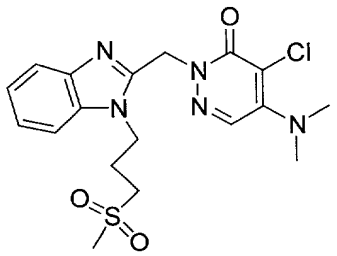
198

A solution of **197** (41 mg, 0.10 mmol) and morpholine (87 mg, 1.00 mmol) in ethanol (1 ml) was heated to reflux for 1 h. The solid formed after cooling was collected and washed by ethanol to give 31 mg (75%) of **198** as a white solid.

^{1}H NMR ($CDCl_3$) δ 2.36-2.40 (m, 2H), 2.98 (s, 3H), 3.42-3.45 (m, 4H), 3.81-3.84 (m, 4H), 4.60 (t, J=7.1 Hz, 2H), 5.67 (s, 2H), 7.27-7.33 (m, 2H), 7.41 (d, J=7.7 Hz, 1H), 7.74 (s, 1H), 7.80 (d, J=7.7 Hz, 1H);

MS m/e 466 (MH^+);

Anal. Calcd for $C_{20}H_{24}ClN_5O_4S$: C, 51.55; H, 5.19; N, 13.03. Found: C, 51.35; H, 5.05; N, 14.86.



199

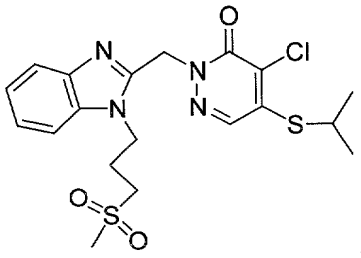
A solution of **197** (41 mg, 0.10 mmol) and dimethylamine (40% aq, 0.2 ml) in ethanol (1 ml) was heated to 120^{0}C in a sealed tube for 1 h. The solvent was removed and the residue purified by reverse phasepreparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 29 mg (68%) of **199**.

^{1}H NMR ($CDCl_3$) δ 2.33-2.38 (m, 2H), 2.97 (s, 3H), 3.14-3.17 (m, 8H), 4.58 (t, J=7.1 Hz, 2H), 5.63 (s, 2H), 7.27-7.32 (m, 2H), 7.39 (d, J=7.7 Hz, 1H), 7.72 (s, 1H), 7.78 (d, J=7.7 Hz, 1H);

MS m/e 424 (MH^+);

Anal. Calcd for $C_{18}H_{22}ClN_5O_3S$: C, 50.99; H, 5.23; N, 16.52;

Found: C, 50.91; H, 4.97; N, 16.37.

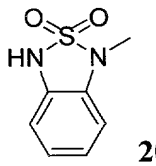


200

A solution of **197** (41 mg, 0.10 mmol), 2-propanethiol (76 mg, 1.00 mmol) and TEA (20 mg, 0.20 mmol) in ethanol (1 ml) was heated to reflux for 1 h. The solvent was removed and the residue purified by reverse phase preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 26 mg (57%) of **200**.

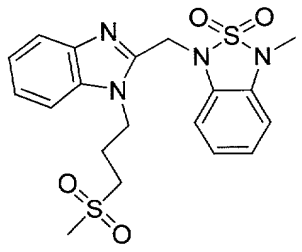
^{1}H NMR ($CDCl_3$) δ 1.44 (d, J=6.6 Hz, 6H), 2.39-2.44 (m, 2H), 2.97 (s, 3H), 3.16 (t, J=7.0 Hz, 2H), 3.64-3.69 (m, 1H), 4.58 (t, J=7.1 Hz, 2H), 5.63 (s, 2H), 7.24-7.31 (m, 2H), 7.39 (d, J=7.8 Hz, 1H), 7.75 (d, J=7.8 Hz, 1H), 7.81 (s, 1H);

MS m/e 455 (MH^+).



201

A solution of N-methyl-1,2-phenylenediamine (2.44 g, 20.0 mmol) and sulfamide (2.11 g, 22.0 mmol) in diglyme (20 mL) was heated to reflux for 1 h. The solvent was removed and the residue taken up in EtOAc (300 ml) and washed with 1N HCl then saturated sodium chloride. The organic layer was dried over $MgSO_4$ and evaporated to give 3.680 g (99%) of **201** as a red viscous oil. The crude product was used for the next reaction without further purification.



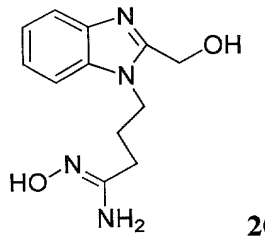
202

Compound **202** was prepared using the same precedure as Compound **25** starting with Compound **10d** and **201.**

^1H NMR ($CDCl_3$) δ 2.23-2.30 (m, 2H), 2.80 (s, 3H), 3.09 (t, J=7.5 Hz, 2H), 3.50 (s, 3H), 4.52 (t, J=8.0 Hz, 2H), 5.13 (s, 2H), 6.76 (d, J= 7.7 Hz, 1H), 6.93 (t, J=7.7 Hz, 1H), 7.02 (t, J=7.6 Hz, 1H), 7.23 (d, J=7.8 Hz, 1H), 7.32-7.44 (m, 2H), 7.44-7.46 (m, 1H), 7.82-7.84 (m, 1H);

MS m/e 435 (MH^+).

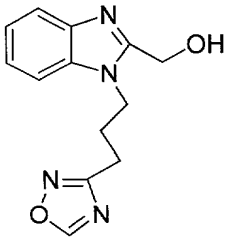
N-Hydroxy-4-(2-hydroxymethyl-benzoimidazol-1-yl)-butyramidine



203

A mixture containing 4-(2-hydroxymethyl-benzoimidazol-1-yl)-butyronitrile, **25a**, (40.0 g, 186 mmol), hydroxylamine hydrochloride (46.5 g, 0.689 mole) and potassium carbonate (51.4 g, 0.372 mole) in ethanol (400 mL) and water (200 mL) was heated at 80^{0}C and stirred overnight. The solvents were removed *in vacuo* and water was added. The white precipitate was collected by filtration, washed with water and dried *in vacuo* to afford N-hydroxy-4-(2-hydroxymethyl-benzoimidazol-1-yl)-butyramidine (35.8 g, 78%) as a white solid:
^{1}H NMR (DMSO) δ 1.97-2.06 (m, 4H), 4.27 (t, 2H, J = 7.4 Hz), 4.72 (s, 2H), 5.44 (br s, 2H), 5.64 (br s, 1H), 7.18 (t, 1H, J = 7.5 Hz), 7.23 (t, 1H, J = 7.5 Hz), 7.57 (d, 1H, J = 7.5 Hz), 7.59 (d, 1H, J = 7.5 Hz), 8.83 (s, 1H);
MS m/e 249 (MH^+);

[1-(3-[1,2,4]Oxadiazol-3-yl-propyl)-1H-benzoimidazol-2-yl]-methanol

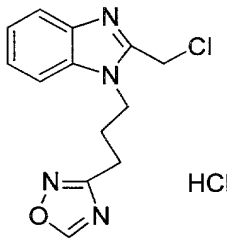


204

A suspension of N-hydroxy-4-(2-hydroxymethyl-benzoimidazol-1-yl)-butyramidine, **203**, (500 mg, 2.01 mmol) in trimethyl orthoformate (5 mL) in the presence of $BF_3.OEt_2$ (50 μL) in a sealed tube was placed in a microwave oven (Smith Creator, Personal Chemistry) and heated at 100^{0}C for 15 min while

stirring, resulting in the dissolution of all the material. The reaction was repeated 5 times. The 6 batches were combined and concentrated *in vacuo*. The residue was treated with 1M HCl (15 mL) and THF (15 mL) and left overnight. Concentration followed by trituration from dichloromethane and recrystallization from isopropyl alcohol and methanol afforded [1-(3-[1,2,4]oxadiazol-3-yl-propyl)-1H-benzoimidazol-2-yl]-methanol (2.28 g, 73%) as a white solid:
^{1}H NMR (DMSO) δ 2.27 (quint, 2H, J 7.4 Hz), 2.95 (t, 2H, J = 7.5 Hz), 4.52 (t, 2H, J = 7.6 Hz), 5.06 (s, 2H), 6.65 (br s, 1H), 7.57 (t, 1H, J = 7.5 Hz), 7.60 (t, 1H, J = 7.3 Hz), 7.79 (d, 1H, J = 7.8 Hz), 8.01 (d, 1H, J = 7.6 Hz), 9.54 (s, 1H);
MS m/e 259 (MH^+);

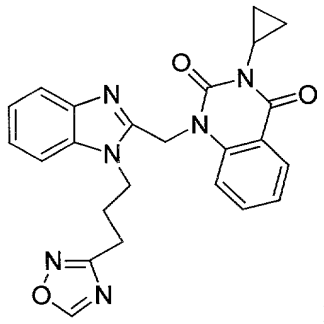
2-Chloromethyl-1-(3-[1,2,4]oxadiazol-3-yl-propyl)-1H-benzoimidazole, HCl salt



205

To a cooled (0^0C) suspension of [1-(3-[1,2,4]oxadiazol-3-yl-propyl)-1H-benzoimidazol-2-yl]-methanol, **204**, (850 mg, 3.29 mmol) in dichloro methane (20 mL) was added thionyl chloride (360 µl, 4.94 mmol). The solution was stirred at 0^0C for 15 min. and then for 1.5 h at ambient temperature. The solution was concentrated *in vacuo* to give 2-chloromethyl-1-(3-[1,2,4]oxadiazol-3-yl-propyl)-1H-benzoimidazole, HCl salt as a white solid in quantitative yield, which was used without further purification:
^{1}H NMR (DMSO) δ 2.27 (quint, 2H, J = 7.5 Hz), 2.95 (t, 2H, J = 7.5 Hz), 4.55 (t, 2H, J = 7.1 Hz), 5.27 (s, 2H), 7.46 – 7.53 (m, 2H), 7.78 (d, 1H, J = 7.9 Hz), 7.89 (d, 1H, J = 7.9 Hz), 9.55 (s, 1H);
MS m/e 277 (MH^+);

3-Cyclopropyl-1-[1-(3-[1,2,4]oxadiazol-3-yl-propyl)-1H-benzoimidazol-2-ylmethyl]-1H-quinazoline-2,4-dione

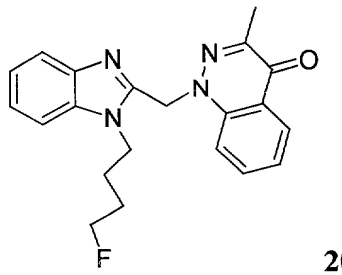


206

To a solution of 3-cyclopropyl-1H-quinazoline-2,4-dione, **159a**, (83 mg, 0.41 mmol) in DMF (6 mL) was added BTPP (269 mg, 0.86 mmol) and the solution was stirred for 15 min. 2-Chloromethyl-1-(3-[1,2,4]oxadiazol-3-yl-propyl)-1H-benzoimidazole, **205**, HCl salt (128 mg, 0.41 mmol) was added and stirring was continued for 1 h. The solution was concentrated and water was added to the residue. The white precipitate was collected by filtration, washed with water and purified by flash chromatography (eluent dichloromethane – ethyl acetate 2:1, 1:1) to afford 3-cyclopropyl-1-[1-(3-[1,2,4]oxadiazol-3-yl-propyl)-1H-benzoimidazol-2-ylmethyl]-1H-quinazoline-2,4-dione (26 mg, 14%) as a white solid:

^{1}H NMR (DMSO-d_6) δ 0.72 – 0.75 (m, 2H), 1.02 – 1.06 (m, 2H), 2.26 (quint, 2H, J = 7.4 Hz), 2.74 – 2.78 (m, 1H), 2.95 (t, 2H, J = 7.4 Hz), 4.49 (t, 2H, J = 7.4 Hz), 5.64 (s, 2H), 7.14 (t, 1H, J = 7.6 Hz), 7.24 (t, 1H, J 7.6 Hz), 7.28 (t, 1H, J 7.5 Hz), 7.49 (t, 1H, J = 8.0 Hz), 7.51 (d, 1H, J = 8.5 Hz), 7.62 (d, 1H, J = 8.1 Hz), 7.68 (t, 1H, J = 7.9 Hz), 8.07 (d, 1H, J = 7.9 Hz), 9.55 (s, 1H);

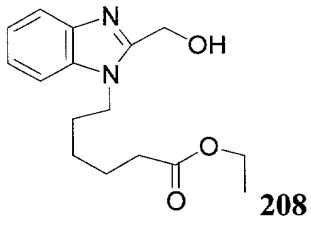
MS m/e 443 (MH^+);



207

To a solution of 3-methyl-1H-cinnolin-4-one (200 mg, 1.25 mmol) (prepared as described by B. Singh, *J. Het. Chem.* **1991**, 881-883) in THF (2 ml) was added BTPP (1.15 ml, 3.75 mmol) and the mixture stirred for 15 minutes at 23°C. Compound **159c** was added and the mixture stirred for 12 h. The solvent is removed and the residue triturated with water. A tan solid was isolated by filtration. The solid is further purified by column chromatography (50% EtOAc in hexanes) as elutant to give 170 mg (37%) of **207**.

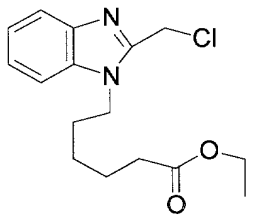
^{1}H NMR (DMSO-d_6) δ :1.68-1.77 (m, 4H), 2.30 (s, 3H), 4.40-4.42 (m, 3H), 4.50-4.52 (m, 1H), 6.04 (s, 2H), 7.16 (t, J = 7.6 Hz, 1H), 7.25 (t, J = 7.7 Hz, 1H), 7.44 (t, J = 7.2 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.60 (d, J= 8.0 Hz, 1H), 7.78 (t, 7.4 Hz, 1H), 7.90 (d, J = 8.9 Hz, 1H), 8.14 (d, J = 8.1 Hz, 1H);
MS m/e 364 (MH^+).



208

Compound **208** was prepared as described for compound **25**, using 2-hydroxymethylbenzimidazole and ethyl 6-bromohexanoate.

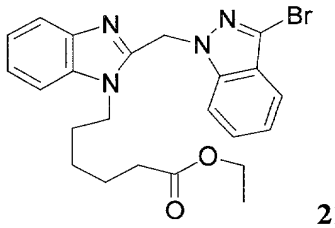
^{1}H NMR (CD_3OD) δ 1.18-1.22 (m, 3 H), 1.42-1.45 (m, 2 H), 1.66-1.69 (m, 2 H), 1.90-1.92 (m, 2 H), 2.30-2.33 (m, 2 H), 4.06-4.10 (m, 2 H), 4.35-4.38 (m, 2 H), 4.89 (s, 2 H), 7.23-7.32 (m, 2 H), 7.51-7.53 (m, 1 H), 7.60-7.63 (m, 1 H);
MS m/e 291 (MH^+).



209

Compound **209** was prepared as described for compound **4c**.

^{1}H NMR (CD_3OD) δ 1.21 (t, J=7.1 Hz, 3H), 1.47-1.54 (m, 4H), 1.65-1.74 (m, 2H), 1.95-2.05 (m, 2H), 2.34 (t, J=7.2 Hz, 2H), 4.03-4.12 (m, 2H), 4.58 (t, J=7.7 Hz, 2H), 5.31 (s, 2H), 7.68-7.72 (m, 2H), 7.83-7.85 (m, 1H), 7.97-8.00 (m, 1H);
MS m/e 309 (MH^+).



210

Compound **210** was prepared as described for compound **25** using compound **4a**.

^{1}H NMR (CD_3OD) δ 1.18-1.32 (m, 5H), 1.46-1.61 (m, 4H), 2.21 (t, J = 7.3 Hz, 2H), 4.04-4.11 (m, 2H), 4.49 (t, J = 7.8 Hz, 2 H), 6.20 (s, 2H), 7.33-7.37 (m, 1H), 7.54-7.60 (m, 3H), 7.64-7.68 (m, 1H), 7.73-7.83 (m, 3H);
MS m/e 469, 471 (MH^+).

BIOLOGICAL ACTIVITY

The antiviral activity of these compounds against respiratory syncytial virus was determined in HEp-2 (ATCC CCL 23) cells that were seeded in 96 well microtiter plates at $1.5x10^4$ cells/100 μL/well in DMEM (Dulbecco's Modified Eagle's Medium) supplemented with penicillin, streptomycin, glutamine, and 10% fetal bovine serum. The cells were incubated overnight at 37 °C, the culture medium was removed, and cells were infected (100 μL volume in medium containing 2% fetal bovine serum) with respiratory syncytial virus Long strain at 5000 plaque forming units/mL. The compounds, 100 μL at appropriate dilution, were added to the cells 1 hour post infection. After incubation for 4 days at 37 °C, the plates were stained with MTT solution (3-[4,5-dimethlythiazol-2-yl]-2,5-diphenyltetrazolium bromide) and incubated for 4 hours at 37 °C. The media was aspirated from the cells and 100 μL/well of acidified isopropanol (per liter: 900 mL isopropanol, 100 mL Triton X100, and 4 mL conc. HCl) was added. Plates were incubated for 15 minutes at room temperature with shaking, and an optical density (OD 540) reading at 540 nanometer (nm) was obtained. The optical density reading is proportional to the number of viable cells. The increase in the number of viable cells reflects the protective, antiviral activity of the compound. Assays comparing MTT staining in uninfected cells containing compound with uninfected cells in the absence of compound provide a measure of cellular toxicity. The control compound in this assay is Ribavirin which exhibits 100% cell protection at 2.5 μg/mL (corresponding to 10.2 μM).

The antiviral activity of compounds, designated as EC_{50}, is presented as a concentration that produces 50% cell protection in the assay. The compounds disclosed in this application show antiviral activity with EC_{50}'s between 50 μM and 0.001 μM. Ribavirin has an EC_{50} of 3 μM in this assay.